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SYMPOSIUM ON HEMORRHAGIC DISORDERS IN INFANTS AND CHILDREN

Guest Editor—I. Newton Kugelmass, M.D.

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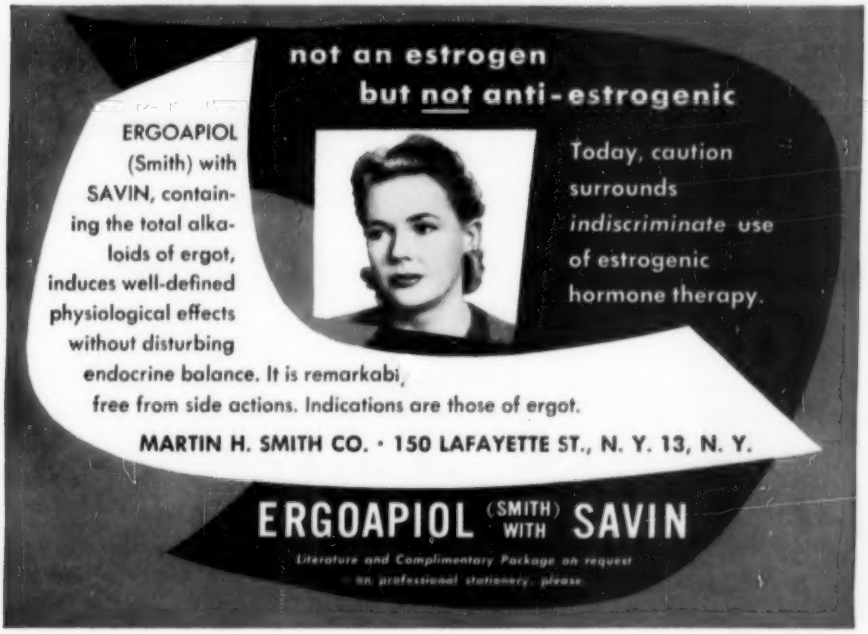
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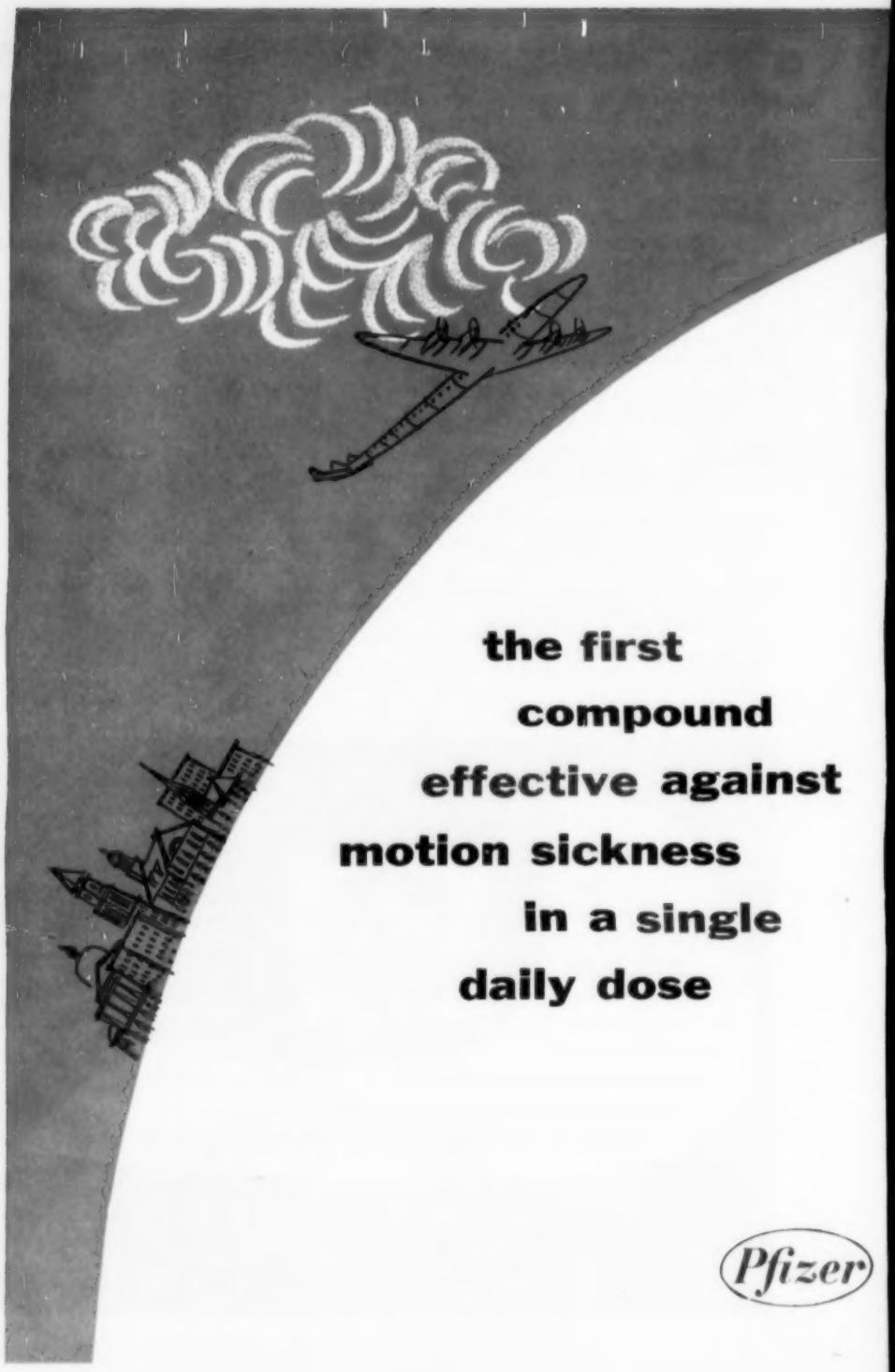

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RECORD OF MEDICINE

VOL. 167 NO. 1 • WHOLE NUMBER 2851 • JANUARY 1954

Symposium on Hemorrhagic Disorders in Infants and Children

EDITORIAL

I. Newton Kugelmass, M.D., Ph.D., Sc.D.

Recent research on blood coagulation stimulated greater interest in hemorrhagic disease but complicated rather than clarified the physiologic basis of clinical medicine. There has been needless repetition of sound experiments, unwise introduction of meaningless terminology, and unjustifiable creation of new theories. Each clotting component has a variety of confusing synonyms; each reaction a host of catalytic reactors. Every tentative hypothesis is being heralded as a tangible discovery. An hypothesis is an inference based on an experimental or clinical observation which is insufficient to prove its high probability. It must not be transposed into fact prematurely. The international experts contributing to this symposium present fundamental advances amenable to clinical application as well as critical statements from which fresh investigations can be planned in this complex field of hemorrhagic disease.

Hemorrhagic problems of infants and children are due to dysfunction in blood-clotting mechanism or in capillary permeability. The first group involves a deficiency in one of the clotting components or an excess in circulating anticoagulants. The second group involves structural or functional changes in the capillaries. The clotting components are well-defined proteins embodying the classic theory of blood coagulation evolved by Hewson, Woolridge, Schmidt, Morawitz, Bordet, Nolf, Howell, Macfarlane, and others.

The reactivity of these compounds following vascular injury is determined by a series of chain reactions. They are catalyzed by protein enzymes to reduce the energy of activation, a phenomenon confirmed experimentally and clinically by Owren, Seegers, Fantl, and others. Each enzyme is accompanied by a coenzyme, each factor by a cofactor, each activator by a precursor, yet all dedicated to the rapid clotting of dissolved fibrinogen. It is Nature's way of maintaining blood fluidity in a closed circulatory system and precipitating fibrinogen following wound injury.

Blood-clotting tests will determine whether the defect is in the clotting mechanism, or in the vascular system, or in both. They are invaluable in differential diagnosis of

hemorrhagic disease. A prolonged clotting time indicates a defect in the clotting mechanism, while a prolonged bleeding time a defect in the capillary endothelium. Yet, a normal clotting time may accompany a partial defect in any clotting component. A prolonged first stage prothrombin test indicates not only a prothrombin deficiency but a possible defect in fibrinogen or globulin accelerators or possible excess of antithrombin. A normal first stage prothrombin test may indicate a defect in antihemophilic globulin or in platelets. An abnormal second stage prothrombin test is truly indicative of prothrombin deficiency. An abnormal prothrombin consumption test may indicate a deficiency of platelets, antihemophilic globulin or excess of antithromboplastin.

The modern classification of hemorrhagic disorders differentiating clotting from vascular defects was presented by the author* at the 1934 Clinical Lecture of the American Medical Association. An evaluation of 500 consecutive hemorrhagic problems in children revealed blood-clotting defects one-third as prevalent as vascular defects. It was apparently due to a greater reserve in clotting components in comparison with the vascular reserve. A child has five times the normal reserve of prothrombin, ten times that of fibrinogen, and twenty times that of calcium, while only twice the vascular reserve. The only time in life when Nature provides the highest possible vascular integrity is at birth, when the capillary resistance is about 500 mm. Hg. in comparison with the adult's resistance of about 150 mm. Hg, designed to protect the infant from birth trauma.

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I. Newton Kugelmass was born in 1896 in New York City. He received his Ph.D. from Johns Hopkins in 1921; Docteur Special in Sciences Physiologiques, University of Brussels, 1922; and his M.D. from Yale in 1925. He has done graduate work in physico-chemical mechanisms of blood disorders at the Sorbonne, University of Zurich, University of Gottingen, University of Leipzig, Pasteur Institute.

Dr. Kugelmass' professional activities include: Professor of Chemistry, Howard College, Birmingham; Research Associate in Pediatrics, Yale University Medical School; Director, Heckscher Institute for Child Health, New York; Director of Pediatric Research, Fifth Avenue Hospital, 1927–35; Attending pediatrician, French Hospital; chief of Growth Clinic, Hospital for Ruptured and Crippled, 1930–33; chief pediatrician, New York City Children's Hospital and School, 1935-40; chief of Children's Clinic for Immunology, French Hospital; appointed consultant nutritionist to Dept. of Health and Dept. of Hospitals, City of New York; consultant pediatrician to Lynn Memorial Hospital, Monmouth Memorial Hospital, Muhlenberg Hospital, New Jersey.

Dr. Kugelmass is a fellow of American Chemical Society, Harvey Society, American Public Health Association, New York Academy of Sciences, Am. Assoc. Mental Deficiency, New York Academy of Dentistry, Society Experimental Biology and Medicine, New York Endocrinological Society, Soc. for Research Child Development, and many other societies and organizations. (*continued on page 12*)

* Kugelmass, I. Newton: J. A. M. A., 102, 204 and 287, 1934.

Clinical Control of Hemorrhagic Disorders in Children*

I. Newton Kugelmass, M.D., Ph.D., Sc.D.†
NEW YORK, N. Y.

PROTHROMBIN DEFICIENCIES

Hemorrhages from the mucous membranes and into the tissues may be inborn or acquired due to interference with the absorption of vitamin K and its utilization by a healthy liver for prothrombin formation. It is revealed by diminished plasma prothrombin, prolonged clotting time, poor clot retraction but normal bleeding time, and normal platelet levels.

Congenital Hypoprothrombinemia: Deficiency of Prothrombin A, B or Ac-Globulin. There are three types of congenital deficiency in the plasma components of the prothrombin complex due to defective protein synthesis in the liver. Absence of prothrombin A is shown by a prolonged prothrombin time when the other two components are present. Absence of Ac-globulin is shown by the inability of the plasma to restore the prothrombin time of the stored plasma to normal.

Each of these inborn defects in the plasma protein causes spontaneous traumatic or operatively induced bleeding from early childhood. The hemorrhage may be severe enough to confuse the disease with hemophilia, hence the designation parahemophilia. Bleeding occurs from the gums, nose, vagina, rectum, and into the skin and internal organs.

The condition does not respond with water soluble vitamin K but occasionally with vitamin K oxide 0.5–1 Gm. intravenously. Arrest hemorrhage by repeated transfusions of fresh whole blood or fresh citrated plasma. The effects last for 6 to 24 hours because of the continuous utilization of borrowed prothrombin during hemorrhage. Check the therapeutic response by prothrombin time determinations.

HYPOPROTHROMBINEMIA IN NUTRITIONAL DEFICIENCIES

Hemorrhagic Disease of the Newborn: The premature and full-term infant acquire prothrombin from the mother. Nevertheless, the newborn develops a physiologic hypoprothrombinemia if the mother's diet was inadequate; if vitamin K was not given to the mother a day before delivery or in the neonatal diet during the first days of life; if there is immaturity of liver function in the newborn; or if there is a neonatal absence of intestinal flora which help form prothrombin. Spontaneous bleeding between the second and sixth day may occur from the gastrointestinal tract into the skin, brain, or from any site if the prothrombin level falls below 15 per cent of the normal.

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* Presented before the Medical Staff, Students and Practitioners of the Hospital Sainte-Justine, University of Montreal, December 2, 1953, on the Annual Pediatric Day.

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Prevent transitory hypoprothrombinemia by oral or parenteral administration of 5 mg. synthetic vitamin K to the mother for several days before delivery, especially in maternal toxemia or in premature or difficult labor. It may prevent intracranial hemorrhage in the newborn. Spontaneous bleeding can be alleviated by intramuscular injection of 2.5 mg. vitamin K at birth. This raises plasma prothrombin in three hours and arrests bleeding thereafter. Bleeding can be arrested more rapidly by transfusing fresh blood 8 cc. per pound of body weight. Fresh Rh negative blood provides more prothrombin than stored blood.

Nutritional Hypoprothrombinemia: Prothrombin is synthesized by the healthy liver if the fat soluble vitamin K is absorbed from the bowel. Vitamin K may be derived from green leaves or may be synthesized in the bowel by bacterial action. An inadequate diet can affect the blood prothrombin concentration in young children. K-avitaminosis may also occur during sterilization of the gut by antibiotic therapy at any age. Mild or moderate hypoprothrombinemia occurs with or without hemorrhagic manifestations. The body becomes unsuspectedly vulnerable to trauma with easy bruising, epistaxis, needle puncture hematomas, or surgical dental bleeding. Determine blood prothrombin levels and administer vitamin K supplements to a balanced dietary.

HYPOPROTHROMBINEMIA IN GASTROINTESTINAL DISEASE

Defective absorption of fat soluble vitamin K induces hypoprothrombinemic bleeding. Fat absorption is impaired in *celiac disease*, *sprue*, *short-circuiting operations*, *regional ileitis*, *intestinal lipodystrophy*, and *bowel obstruction*. Bile salts fail to enter the intestine in *obstructive jaundice*, *biliary fistula*. Faulty absorption also occurs in hyperperistalsis of *chronic dysentery*, *ulcerative colitis*.

Offer water soluble vitamin K to patients with intestinal disorders orally or parenterally. If fat soluble vitamin K is used give bile salts simultaneously to assure absorption. Plasma prothrombin determinations should be used as guides to treatment. Prescribe vitamin K for hypoprothrombinemia below 75 per cent normal preoperatively to prevent depression of prothrombin to 25 per cent normal, the critical level for bleeding.

HYPOPROTHROMBINEMIA IN LIVER DISEASE

Prothrombin cannot be synthesized by the liver in hepatic disorders even though fat soluble vitamin K is abundantly absorbed. Hemorrhages from mucous membranes into the skin and internal organs occur in *postanesthetic liver injury*, in *acute yellow atrophy*, in Laennec's *cirrhosis*, in infiltration with *malignant or leukemic cells*, in *chemical poisoning* with phosphorus, chloroform or arsenic, in traumatic or *surgical shock*.

Bleeding can be relieved with large transfusions of fresh blood or 100 cc. of plasma. The risk of infectious hepatitis from pooled plasma should be considered. Intramuscular vitamin K is ineffective if there is severe liver dysfunction. Administer vitamin K_1 intravenously in the presence of jaundice or possible vitamin K deficiency.

HYPOPROTHROMBINEMIA IN DRUG THERAPY

Anti-vitamin K activity by *dicumarol, salicylates, quinine, tromexam, phenylinandione* et cetera suppresses the formation of prothrombin in the liver. There is no direct action on prothrombin. Overdosage of dicumarol leads to severe hemorrhages from the skin, mouth, and even into the brain. Salicylates may reduce plasma prothrombin sufficiently to cause bleeding since salicylic acid is a degradation product of dicumarol. Anticoagulation therapy without frequent determinations of prothrombin actively results in abnormal bleeding.

Normal prothrombin levels can be restored promptly by discontinuation of the drug, administration of vitamin K and supportive transfusions until the action of the drug has been neutralized. Emergency transfusion of fresh, whole blood supplemented by 500 cc. fresh plasma will control bleeding temporarily. The effect lasts about five hours since the prothrombin supplied by blood and plasma is rapidly diluted in the circulation. A simple transfusion will promptly raise the prothrombin level to 30 per cent, while vitamin K will take several hours to increase the prothrombin. After the transfusion administer massive doses of vitamin K without delay.

Natural vitamin K_1 oxide is more effective than water-soluble compounds. Dissolve 1 cc. oil solution of 1 Gm. vitamin K_1 oxide in 20 cc. ethyl alcohol. Inject the solution slowly under the surface of 500 cc. 5 per cent dextrose while shaking vigorously. Inject the stable emulsion intravenously within two hours. An alternate method is to inject 150 mg. of vitamin K intramuscularly daily. Offer bile salts in the presence of liver or biliary tract disease. It must be remembered that the toxicity of vitamin K; i.e., 180 mg. orally may cause vomiting and porphyrinuria.

FIBRINOGEN DEFICIENCY

Severe bleeding may follow minor injuries from birth due to congenital absence of fibrinogen or develop de novo due to acquired loss of fibrinogen in systemic disease. In either case the clotting time and bleeding time are prolonged, the clot retraction poor, and the plasma fibrinogen absent or decreased. Each is a clinical curiosity yet the patient survives by compensatory mechanisms of hemostasis.

Congenital hypofibrinogenemia. Complete absence of fibrinogen is usually confused with hemophilia or hypoprothrombinemia. It is inherited by children of either sex derived from marriages of first cousins. The newborn bleeds profusely from the umbilicus, the infant after eruption of the milk teeth and the child after slight trauma. Once the bleeding starts, it continues for hours or days. When the bleeding ceases, it seems to take a long time for an attack to recur. Partial congenital absence of fibrinogen is probably more common than realized because of failure to determine the level of plasma fibrinogen. Partial absence of fibrinogen is evident when only a few strands of fibrin are formed within the normal clotting time. The fine fibrin filament, although present, is insufficient to bind the cellular elements into a real clot. An abnormal level of fibrinogen may also be suspected from a retarded erythrocyte sedimentation rate—the less the fibrinogen, the slower the rate.

Control hemorrhages by transfusions of whole blood or fresh plasma. More effective is the intravenous injection of Cohn plasma fraction I, which provides 60 per cent fibrinogen. Administration of 200 mg. at the onset of bleeding will maintain blood fibrinogen at the normal level of 200 mg. per 100 cc. Since the child's blood level of replaced fibrinogen gradually diminishes within 30 days to about 50 mg. per 100 cc., the critical level for bleeding, the same dose of plasma fraction I should be injected at monthly intervals.

Acquired Hypofibrinogenemia. Symptomatic hypofibrinogenemia occurs in deficiency diseases, e.g., scurvy, pellagra, and pernicious anemia; in bone marrow diseases, especially myelogenous leukemia and polycythemia; in liver diseases where extensive injury reduces fibrinogen formation; and, of course, in severe infectious diseases such as scarlet fever, pneumonia, tuberculosis and brucellosis which destroy liver structure and increase circulating fibrinolysin. Transfuse with whole blood or fresh plasma or Fraction I (Cohn) 150 cc. lyophiliased fibrinogen 1 Gm. in 150 cc. of 5 per cent dextrose.

Hypofibrinogenemia from increased Fibrinolysin. Treat fibrinogen deficiency hemorrhage from increased fibrinolysis as indicated above for hypofibrinogenemia. Fibrinolysis is an enzyme dissolution of fibrinogen strands. It occurs normally in fibrinogen metabolism and in tissue repair. Mild degrees of fibrinolysis in plasma accompany exercise, anxiety, the alarm reaction, epinephrin injection. Marked fibrinolysis causing hemorrhage may follow transfusion reactions, hemolytic crises, hemorrhagic shock, severe injury, and liver disease.

EXCESSIVE ANTICOAGULANTS

Hemorrhagic Diathesis from circulating Anticoagulants. Several hemophilic-like disorders predominant in the female are characterized by such potent anticoagulants that the profuse and persistent bleeding cannot be overcome even by massive transfusions. Not only is the clotting time prolonged but the patient's blood will prolong the clotting time of normal blood. It occurs in heredofamilial plasma defects, in the course of hemophilia, or in excessive irradiation with x-ray.

Circulating anticlotting compounds shift the reversible chain reactions in the clotting mechanism in the opposite direction inhibiting the formation of fibrin. Blood coagulation cannot occur when the rate of production of clotting compounds is less than the rate of neutralization by opposing inhibitors. Excessive circulating anticoagulants thus produce hemorrhagic disease simulating hemophilia. We know of nothing to give as an antidote to their action.

Hemorrhagic Diathesis from Hyperheparinemia. The blood shows a heparin-like substance by protamine titration, prolonged clotting and bleeding time, and diminished platelets. The hemorrhagic disorder may occur in leukemia, aplastic anemia, lymphosarcoma, Hodgkin's disease, nitrogen mustard therapy, and ionizing irradiations.

Control bleeding with intravenous injections of protamine sulfate 0.3 mg. per Kg. of body weight in 50 cc. sodium chloride solution every 24 hours or inject less toxic toluidine blue dye 2.5 mg. per Kg. of body weight daily. Provide platelets

by repeated fresh whole blood transfusions until recovery. Neutralize overdosage of heparin therapy by injecting intramuscularly 1 mg. protamine per Kg. of body weight in 200 cc. saline over a period of 10 minutes. It combines with heparin in the ratio of 2:1 and inactivates the anticoagulating properties in minutes.

THROMBOPLASTINOGEN DEFICIENCIES

Hemophilia is a lifelong tendency to excessive hemorrhage into the skin, mouth, gastrointestinal tract and joints, transmitted by daughters of hemophiliacs to their sons. The blood shows a greatly prolonged clotting time and hardly any prothrombin consumption or thromboplastinogen activity during hemorrhagic cycles but a normal prothrombin concentration, platelet count, bleeding time and capillary resistance.

Local Hemostatics. Control mild hemorrhages by compression with natural hemostatics: fresh human serum, freshly cut meat and placental, lung or brain extract; or with artificial preparations: thromboplastin solution, hemostatic globulin, fibrin foam or gelfoam saturated with epinephrin or topical thrombin. Remove loose clots adherent to the bleeding site by means of saline solution. Approximate the edges without sutures. Apply cold dressings of human thrombin or other hemostatic to the site of bleeding. Keep the hemostatic agent cold to contract the affected blood vessels. Offer ices for mouth bleeding. Apply an ice bag to a contusion or a bleeding joint.

Blood and Plasma Transfusions. Control severe hemorrhages by repeated transfusions of 250 cc. fresh whole blood or fractionated human plasma (fresh, frozen or dried), every eight hours. Plasma is preferable to blood transfusions because it provides twice the amount of thromboplastinogen present in whole blood. Raise the level of this clotting factor adequately by injecting large volumes of plasma at a time to arrest or prevent bleeding or to prepare the patient for surgery. Plasma can be given in greater amounts than whole blood without inducing untoward reactions. Beware of the greatest danger in hemophilia from pressure of hematomas upon vital structures. Relieve pressure symptoms by aspiration or drainage after administration of fresh or lyophilized plasma. It is more effective than the antihemophilic globulin Fraction I (Cohn) because the former maintains potency for months while the latter loses it in days or weeks. A potent fraction of 200 mg. equivalent to 100 cc. blood arrests persistent bleeding promptly. A hemophilic may become refractory to each of these colloids—blood, plasma, or globulin—capable of producing neutralizing antibodies.

CALCIUM DEFICIENCIES

Hypocalcemia never causes hemorrhage. There is no decrease in blood-calcium level or calcium ion concentration in any hemorrhagic disorder. Calcium deficiency in any disease never leads to bleeding, not even in infantile tetany where calcium levels are greatly depressed. Calcium ions and calcium co-factor are indispensable for the reaction between prothrombin complex and accelerator globulin. There is always adequate calcium for this catalytic reaction. Nevertheless, calcium salts

are often prescribed in hemorrhagic disorders in order to arrest bleeding. There is no experimental or clinical evidence that the treatment is ever effective. But it has been demonstrated that the administration of calcium compounds decreases capillary permeability in all types of vascular purpuras.

PLATELET DEFICIENCIES

Multiple hemorrhages into the skin or from the mucous membranes are associated with a reduced platelet count, a prolonged bleeding time, poor clot retraction, and increased capillary fragility. Effective treatment depends upon absolute differentiation between the essential or primary purpura and the symptomatic or secondary purpura. The more complete the work-up of a case, the less likely the diagnosis of essential purpura.

In the essential type, a splenic factor acts on the bone marrow to prevent either the development of megakaryocytes from the reticuloendothelial system or the development of platelets from mature megakaryocytes. In the symptomatic or common type of purpura, the low platelet level is incidental to some underlying disease in the bone marrow or spleen.

Essential Thrombocytopenia

Transfusion. Control hemorrhage by direct transfusions of whole blood, freshly drawn at 2 to 5 day intervals from platelet-rich polycythemic donors. It will temporarily improve the platelet level, bleeding time, and cell volume. Platelet transfusions with siliconized apparatus are most effective but repeated injections may lead to the development of platelet agglutinins and decreased survival time of transfused platelets. Use fresh blood with normally dispersed platelets for thrombocytopenia and stored blood with agglutinated platelets for blood replacement.

Hormones. When transfusions fail to control bleeding in the acute fulminating or chronic recurrent case, use ACTH or cortisone. These hormones are effective not only in the temporary emergency of a serious hemorrhage but in the preoperative preparation for splenectomy. A remission in the thrombocytopenia and an improvement in capillary fragility can be expected. Hormone therapy is also effective in 1 out of every 3 splenectomized patients with hemorrhagic relapses.

Splenectomy. Tide over an acute attack with transfusions because of the high mortality of emergency splenectomy. Control moderate purpura with hormonal therapy and transfusions for four "long" months unless life is threatened. During an hemorrhagic episode, a child has a marked tendency to spontaneous remission. Consider splenectomy as a lifesaving procedure if conservative management fails in essential thrombocytopenia. It will remove the splenic factor responsible for the low platelet levels provided sternal marrow smears reveal adequate numbers of megakaryocytes.

Splenectomy should be performed during the quiescent stage of the disease when the operative mortality is low. Bleeding ceases dramatically after operation. The platelets rise to high levels for a week or two before falling to normal or low levels.

The bleeding time is more favorably affected than the number of platelets or the retractility of the clot. Splenectomy thus improves capillary resistance.

Search for accessory splenic tissue, liver, and mesentery lymph nodes. As little as 5 Gm. of splenic tissue may precipitate a relapse. Locate aberrant splenic tissue by thorotrast visualization. Serial blood transfusions may be necessary when hyperfunctioning reticuloendothelial phagocytes are present in the liver and lymph nodes.

Splenectomy is contraindicated if the blood picture suggests aplasia with severe anemia and neutropenia or if the marrow shows diminished platelets and/or megakaryocytes. The chances for continued recovery are about 30 per cent following medical treatment and 70 per cent following successful splenectomy. Death may occur from severe external hemorrhage, bleeding into vital tissues, marked anemia, or extreme exhaustion.

Symptomatic Thrombocytopenia

Treatment of the Bone Marrow Defect. In aplastic anemia all parts of bone marrow, including the megakaryocytes, are affected. Severe secondary purpura from markedly reduced platelets respond to supportive replacement of fresh citrated blood. Polycythemic blood is most effective, bank blood least.

In hypoplastic anemia accompanying gastrointestinal or allergic disorders, there may be platelet deficiency from marrow hypoplasia. Secondary purpura will clear promptly with correction of the nutritional deficiency. Analyze the patient's diet for inadequate utilization of amino acids, liver extract, vitamin B and C complexes, trace minerals, and unsaturated fatty acids.

In displacement thrombocytopenia accompanying leukemia, myeloma, metastatic carcinoma, etc., there is an obliteration of megakaryocytes and other marrow elements. Detect the condition by bone marrow aspiration. Control secondary purpura by fresh blood transfusions, ACTH and cortisone, and specific treatment of the primary marrow disorder.

In toxic thrombocytopenia, damage to megakaryocytes in the marrow reduces circulating platelets. It occurs in acute infections, chemical poisoning, drug and food allergy, irradiation, insect bites, and burns. Detect toxic injury by supravital staining of fresh marrow. Eliminate the source of offense. Give fresh blood transfusions; hesperidine 100 mg. and ascorbic acid 500 mg. daily; and specific treatment of underlying disease.

Treatment of the Splenic Defect. Secondary thrombocytopenia may be due to hypersplenism accompanying some constitutional disease. The enlarged spleen becomes overactive in the destruction of platelets, but the marrow shows an increase in mature megakaryocytes with normal platelet formation.

An epinephrin test confirms platelet hypersequestration in the spleen in Banti's disease, Felty's syndrome, Gaucher's disease, splenic Hodgkin's granuloma, congestive splenomegaly, myocardial decompensation, and acute infectious splenic tumor. This group of acute or chronic splenic disorders responds to emergency splenectomy. It will prevent sudden crises, fatal hemorrhage, or chronic invalidism.

Hereditary Purpuras

Hereditary Thrombocytopenia is a quantitative platelet defect. The blood of males and females of certain families shows relatively few platelets, usually less than 20,000 per cu. mm. But the platelets are qualitatively very effective, dissociating rapidly unless there be intercurrent infection or systemic disease. Tide them over with fresh blood transfusions. Splenectomy is certainly contraindicated.

Hereditary thromboasthenia is a qualitative platelet defect. The blood of males and females of some families shows relatively normal numbers of platelets defective qualitatively. They dissociate too slowly to be effective for blood clotting. Consequently, there are prolonged bleeding, failure of clot retraction, excessive bleeding, easy bruising, and recurrent purpura. Treat an hemorrhagic episode with fresh whole blood transfusions from polycythemic donors. There is a natural tendency to spontaneous improvement at maturity. Splenectomy is ineffective and harmful.

CAPILLARY DEFECTS

Spontaneous hemorrhages into the skin and viscera and from the mucous membranes occur in hereditary and acquired defects of the capillary endothelium. Blood oozes or flows from abnormalities in the vascular wall because of increased capillary permeability. The patient shows increased capillary fragility and prolonged bleeding time but normal blood clotting mechanism.

Hereditary Purpuras

Hereditary Telangiectasia. Familial capillary hemorrhage is transmitted by either parent to both sexes. Repeated bleeding occurs from localized dilatations of capillaries with thin walls that cannot contract in the nose, mouth, and stomach. Consequently, the bleeding time is prolonged in the affected area but normal from other capillaries. Arrest nosebleeds, the common defect, with tampons of thrombin or fibrin foam. Cauterize bleeding points with a chromic acid bead, electrocoagulation, or submucous injection of 5 per cent quinine and urethane. Offer hesperidin or rutin 100 mg. with ascorbic acid 250 mg. to decrease capillary permeability and ferrous sulfate to correct hypochromic anemia. When surgery is contemplated, no special procedures to prevent bleeding are required because all clotting components are normal.

Constitutional Thrombopathy

Recurrent spontaneous hemorrhage is an heredofamilial tendency transmitted by either parent to sons and daughters. There are prolonged bleeding times and positive tourniquet test but normal clotting time, efficient clot retraction, and adequate platelet levels. The persistence of the bleeding simulates hemophilia, hence the difficulty of diagnosis in the male. Control accessible bleeding with thrombin and fibrin foam. Arrest inaccessible bleeding with fresh whole blood transfusions. Offer antibiotics prophylactically to combat infections detrimental to capillary endothelium and hesperidin 100 mg. and vitamin C 500 mg. daily to decrease capillary permeability.

Nutritional Purpuras

Scurvy. Ascorbic deficiency may be latent or manifest. Infants develop swollen, bleeding gums, painful subperiosteal hemorrhages, and hematuria. Adults develop hemorrhage into the orbital fossa, mucous membranes, and skin. All clotting tests are normal but capillary fragility is markedly increased. Clear hemorrhagic symptoms with 250 mg. ascorbic acid daily. Decrease capillary permeability with 100 mg. hesperidin daily. Prevent recurrence with an adequate diet abundant in raw protective foods.

Allergic Purpuras. Three types of allergic purpuras occur individually or in combinations. *Purpura simplex* is an hereditary tendency to easy bruising found especially in infants and adolescent girls of allergic families. Symmetrical purpuric spots appear about the hair follicles in the upper and lower extremities especially after an attack of headache, fever, and malaise. If severe, the bleeding may be intramuscular, subperiosteal or visceral, accompanied by allergic skin lesions. *Henoch's purpura* begins with vomiting, fever, diarrhea, abdominal distention, and colic before any purpuric eruptions develop. The allergic gastrointestinal disturbance is produced by an urticarial serohemorrhagic effusion into the intestinal wall. It is accompanied by ecchymoses, hematemesis, melena, or hematuria. *Schönlein's Purpura* develops as a migratory disturbance produced by periarticular effusions. The affected joints become purpuric, painful, swollen, tender, hot, and red. There is an accompanying edema of the face and eyelids and urticaria over the trunk. Offer antihistamines not salicylates, since the condition is unrelated to rheumatic fever.

Desensitization. Determine the sources of allergic offense from the history and skin tests. Relieve the attack with 1 cc. epinephrine in oil (1:500) intramuscularly twice daily. Decrease capillary permeability with 500 mg. of vitamin C and 200 mg. of hesperidin daily, and with 10 per cent calcium gluconate 5 to 10 cc. intramuscularly three times a day. Decrease sensitivity to external agents with an appropriate antihistamine until skin tests determine the causative allergens. Inject histamine diphosphate as a desensitizing agent, beginning with 0.1 mg. subcutaneously and gradually increasing to 1 mg. at four day intervals. In severe cases add histamine 2 mg. to parenteral fluids and continue a weekly 1 mg. maintenance dose.

Infectious Purpuras

Hemorrhagic infections. Capillary injury by toxins produces purpura in scarlet fever, measles, pneumonia, diphtheria, acute glomerular nephritis, typhus, smallpox, spotted fever, meningococcic meningitis. Purpura may also be produced by bacterial emboli in subacute bacterial endocarditis, typhoid fever, and meningococcic septicemia. The organisms can often be demonstrated in the purpuric skin lesions. An initial reduction in the platelets level is gradually overcome in the later stages of the infection. Treat the underlying infection.

Purpura fulminans. Large symmetrical ecchymoses appear over the skin surfaces. However, bleeding never occurs from mucous membranes or from internal viscera. The blood platelets are normal, but capillary resistance is diminished. The centers of vascular innervation in the spinal cord are involved. The child usually succumbs

within four days, although purpura complicating scarlet fever may be relieved by daily intravenous infusions of the amino acid methionine 3 Gm. in 500 cc. saline.

Waterhouse-Friderichsen Syndrome. Bilateral hemorrhage into the adrenal glands produces cyanosis, shock, and fever. Respirations become rapid and labored and the child sinks into a deep coma. Petechial and purpuric spots appear over the entire body and coalesce into ecchymoses. In the newborn the adrenal hemorrhage is induced by birth trauma. In the infant and older child, the condition is precipitated by infection—meningococcic, streptococcic, pneumococcic or diphtheritic. Treat this desperate condition without delay. Combat infection with sulfas and antibiotics. Reinforce intravenous infusions of plasma, dextrose, and saline with adrenocortical extract 10 to 30 cc. daily. Add vitamin K for the newborn and vitamin C for the older child.

Mechanical Purpuras

Capillary bleeding may be induced in a normal individual in any region of the body subjected to sudden increase in venous pressure. Treat the underlying condition to overcome vascular purpura. *Whooping cough* may produce bleeding from the conjunctivae, nose, eyelids and bronchi. *Rheumatic heart disease* may cause epistaxis or petechial hemorrhages in the extremities. *Convulsions* may produce purpura in the head and upper extremities from increased pressure within the blood vessels. *Uremia* may cause cerebral, retinal, and intestinal hemorrhage from the concurrent hypertension. *Leukemia* may cause bleeding by infiltration of the walls of the blood vessels. Extremes of *heat* or *cold* may cause exposed area to bleed. *Chronic anoxemia* of a part of the body may lead to localized petechial hemorrhage. *Trauma* may induce vascular purpura in the affected region. Prolonged standing may cause *orthostatic purpura* in lower extremities if the capillaries are defective.

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I. Newton Kugelmass (*continued from page 2*)

Books by Dr. Kugelmass include: *Clinical Nutrition in Infancy and Childhood*, the *Story of Infancy*, *Growing Superior Children*, *Pediatric Nutrition*, *Blood Disorders in Children*, *Principles and Practice of Pediatrics*, *Clinical Pediatrics*, *New Nutrition in Pediatric Practice*. Doctor Kugelmass has contributed to the following publications: A. M. A. Journal Pediatrics, Journal Biological Chemistry, Am. J. Diseases Children, American Journal Digestive Diseases and Nutrition, American Journal of Mental Deficiency, et cetera.

Hereditary Defects of Blood Coagulation

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Every pediatrician is familiar with the problems raised by children with abnormal bleeding. His first concern is to decide whether the hemorrhage is due to some underlying disease or to a primary hemorrhagic diathesis. In children purpuric bleeding is more often symptomatic than primary, and bleeding of the clotting defect type is, apart from vitamin K deficiency, more often primary than symptomatic. Thus, the commoner hemorrhagic states can usefully be divided by clinical observation into the purpura group, characterized by petechia, ecchymoses, and spontaneous oozing from the gums and nose, and a hemophilia-like group characterized by prolonged bleeding from injuries, massive bruising, and deep tissue hemorrhages and hemarthroses. It is mainly these latter conditions which will be considered here.

It is now apparent that there exists a number of hemorrhagic states caused by basically different clotting defects, the proper identification of which is clinically important. Their symptomatology is of little help in differentiation since any severe clotting defect will produce in time a clinical picture indistinguishable from hemophilia. Most of these defects are hereditary, and, since the mode of inheritance differs from one condition to another, diagnostic help can often be obtained from a carefully constructed family tree. The final differentiation must, however, be derived from laboratory findings, and recent advances in technical methods have provided the means to recognize distinct entities previously diagnosed indiscriminately as "hemophilia." Such differentiation is of practical value because methods of treatment which may be effective in one are useless in another, and any assessment of prognosis for the patient and his offspring depends on an accurate diagnosis.

The clotting system is complex, involving a chain of reactions among at least nine factors, all of which are present in the blood. The subject has been confused by multiple terminology and, for the sake of clarity, a list of synonyms for the terms used here is given in table I. There is good evidence that the first stages in coagulation are concerned with the generation of thromboplastin within the blood. This thromboplastin then activates prothrombin in the presence of calcium, forming thrombin which reacts with fibrinogen to form fibrin. It is the study of the thromboplastin-forming system which has provided advances in the understanding of the hereditary clotting defects, since faults in this system account for five of the six conditions in this group.

At least six factors appear to be concerned with the development of thromboplastic activity, these being platelets, antihemophilic globulin, Christmas factor, factors 5 and 7, and calcium. The platelets provide an active lipoid and perhaps other factors which have not been clearly identified yet. Antihemophilic globulin is normally present in the globulin and fibrinogen fractions of the plasma but is deficient in hemophilia. Christmas factor also is present normally in the plasma, but is deficient in "Christmas disease." Christmas factor is relatively stable, is

TABLE I

Some Synonyms for the Factors Concerned in Thromboplastin Generation

Factor 5 (Owren 1947)	Factor 7 (Koller, Loeliger and Duckert 1951)
Thrombogen (Nolf 1908)	Stable component (Stefanini 1953)
Labile factor (Quick 1943)	Proconvertin—convertin (Owren 1951)
Prothrombin accelerator (Fantl & Nance 1948)	Serum prothrombin conversion accelerator (S.P.C.A.) (Alexander & de Vries 1949)
Proaccelerin—accelerin (Owren 1950)	Prothrombin conversion factor (Owen & Bollman 1948)
Plasma accelerator globulin (Ware, Guest and Seegers 1947)	Cothromboplastin (Mann & Hurn 1950)
Antihemophilic Globulin (Lewis et al 1946)	Christmas Factor (Biggs et al 1952)
Thromboplastinogen (Quick 1947)	Plasma thromboplastin component (P.T.C.) (Aggeler et al 1952)
Thrombocytolysin (Brinkhous 1947)	Factor 9 (Koller 1953)
Plasma thromboplastic factor (Stefanini 1953)	
Factor 8 (Koller 1953)	

found in serum as well as plasma, and is adsorbed by $BaSO_4$ and $Al(OH)_3$; antihemophilic globulin is labile, is not present in serum, and is not adsorbed by $BaSO_4$ or $Al(OH)_3$. Factor 5 is a labile substance found in normal plasma, but disappears rapidly on storage. Factor 7 is a stable substance found in plasma and serum. Factor 7 is adsorbed, and factor 5 is not adsorbed, by $BaSO_4$ or $Al(OH)_3$.

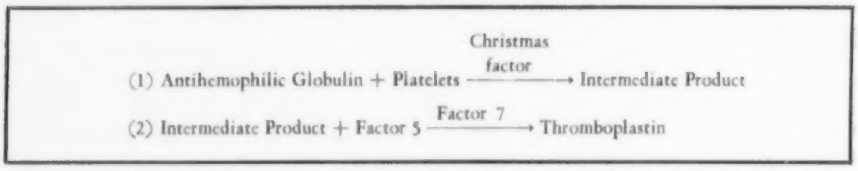

FIG. 1. The probable interrelationship of the factors responsible for thromboplastin generation in the blood.

Evidence suggests that contact with a foreign surface such as glass or damaged tissue sets this thromboplastin-forming mechanism in motion. Under the influence of some physical change induced by contact, Christmas factor reacts with antihemophilic globulin and platelets to form an intermediate product. This intermediate product then reacts with factors 5 and 7, and the final product, called "thromboplastin" here, activates prothrombin (fig. 1). Thromboplastic activity normally takes several minutes to appear, this interval constituting the greater part of the clotting time as ordinarily measured; it then reaches a maximum and rapidly declines. During this process, antihemophilic globulin and factor 5 are used up, whereas Christmas factor and factor 7 are not consumed, and remain present in the serum.[6]

This mechanism and the efficiency of its component parts can be studied by means of the thromboplastin generation test.[5] In this test platelets are mixed with plasma which has been treated with $Al(OH)_3$ to remove prothrombin, factor 7, and Christmas factor. This mixture is incubated with serum that contains factor 7 and Christ-

mas factor but not antihemophilic globulin, factor 5, or prothrombin. If all the components are normal, thromboplastic activity appears in the incubated mixture, being demonstrated by adding samples to normal recalcified plasma and recording clotting times as in the one-stage prothrombin time test. The thromboplastin at its maximum activity will clot the plasma in eight seconds or less. Any defect is shown by a delay in thromboplastin formation or a reduction in the amount formed, and by deriving the platelets, plasma, or serum from the patient's blood in different tests any defect can be located. Thus, inactivity of the platelet factor is immediately apparent; a deficiency of either factor 5 or antihemophilic globulin is indicated by inactivity of the plasma component, and a deficiency of either factor 7 or Christmas factor is indicated by inactive serum. The distinction between members of these two pairs of factors can be made by applying the prothrombin time test, since a deficiency of either factor 5 or 7 prolongs the prothrombin time, whereas a deficiency of antihemophilic globulin and Christmas factor does not (table II).

TABLE II

The Differentiation of Some Hereditary Coagulation Defects

Condition	Defect	Inheritance	Prothrombin Time	Thromboplastin Generation Test	
				Plasma	Serum
Hemophilia	A.H.G. deficiency	Sex-linked recessive	Normal	Abnormal	Normal
Christmas disease	Christmas factor deficiency	Sex-linked recessive	Normal	Normal	Abnormal
"Parahemophilia"	Factor 5 deficiency	Non-sex-linked	Abnormal	Abnormal	Normal
"Hypoproconvertinemia"	Factor 7 deficiency	Non-sex-linked	Abnormal	Normal	Abnormal

In clinical practice hemorrhagic states due to a deficiency of any of these factors may be encountered. In platelet deficiency the tendency to bleed is complex, being not only due to defective thromboplastin generation but to capillary defects responsible for spontaneous superficial hemorrhage. Numerical deficiency of platelets reduces the amount of thromboplastin formed but unless very extreme does not delay the onset of its formation. In thrombocytopenia the simple clotting time of the blood is usually normal because it is mainly controlled by the time at which thromboplastin first appears; but the amount of prothrombin converted is reduced, because less than the normal amount of thromboplastin is formed.[19] Thrombocytopenia in children, though usually secondary to leukemia or to some infective or toxic process, may be idiopathic or occasionally hereditary, the inheritance being non-sex-linked.[40, 41] There is however a rare condition in which the platelets, though present in normal numbers, are qualitatively defective. This so-called thromboasthenia produces the same clinical manifestations as thrombocytopenia, but the platelet count is normal. Clot retraction, prothrombin consumption, and thromboplastin generation are all reduced, and the platelets are often larger than normal and of bizarre shapes. The condition may be secondary to such diseases as leukemia

or polycythemia but may be idiopathic or occasionally hereditary. It must not be confused with von Willebrand's disease which is an inherited (dominant) defect of the capillaries, indicated by a prolongation of the bleeding time, usually the only abnormal finding.[3]

Deficiency of antihemophilic globulin, Christmas factor, factor 5, or factor 7 will produce similar clinical manifestations. There will be a history of persistent bleeding from trivial injuries, often of hematuria and less frequently of gastrointestinal bleeding. Sooner or later in the majority of cases there is hemorrhage into the joints, at first produced by a definite strain or blow, later appearing on the least provocation as the joint structure becomes destroyed by the effects of hemorrhage. Massive effusions of blood into the tissues may take place, usually the result of trauma, sometimes following some minor local infection. Such effusions may cause ischemia, paralysis, or gangrene, and in the region of the mouth or throat, they are particularly dangerous for they may obstruct respiration. In most cases, the thromboplastin-factor deficiency is hereditary or at least congenital, and the history of bleeding, therefore, goes back to infancy. In a few instances, the deficiency has been acquired in late childhood or adult life and in these the etiology is obscure.

Of these conditions, hemophilia, being the commonest, is the most important. Hemophilia is a hereditary deficiency of antihemophilic globulin, the inheritance being of the sex-linked recessive type and the defective gene situated on the X chromosome. Active bleeding occurs in the affected male but not in the affected female, unless she is homozygous for the condition. The family history may reveal the occurrence of hemophilia in the patient's brothers, and in uncles, male cousins, grandfather, and other male collaterals on the maternal side of the family only. Any departure from this mode of inheritance should raise doubts regarding the diagnosis. It must be remembered, however, that from 20 to 30 per cent of hemophilia cases may have no family history, either because the condition has arisen *de novo* in the patient or in his mother, or because the family contains only a few males who have escaped the condition by chance. From the point of view of genetic prognosis, it can be stated that all the daughters of a hemophilic male are carriers of the condition and each child of a female carrier has an equal chance of being normal or affected. No reliable laboratory test revealing the carrier state in females has yet been produced.[23] Homozygous females are the offspring of a male hemophilic and a female carrier, usually resulting from cousin intermarriage in hemophilic families. They are, naturally, extremely rare.[15, 21, 31]

A deficiency of antihemophilic globulin delays the onset of thromboplastin generation and reduces the amount formed. Therefore, the clotting time usually is lengthened. A number of cases have been described, however, in which the clotting time was normal, or nearly so, suggesting that this test is not a sensitive index of the liability to bleed, or of the level of antihemophilic globulin in the blood.[22] The prothrombin consumption test is a more sensitive, if nonspecific, test and was abnormal in most of these cases. The thromboplastin generation test has shown a marked deficiency of antihemophilic globulin in all such patients examined. The prothrombin time is normal in hemophilia since antihemophilic globulin is not required for the reaction between brain extract and prothrombin.

Within the last two years it has become evident that a proportion of cases diagnosed as hemophilia are due to a deficiency not of antihemophilic globulin but of some other factor. Seven such cases examined by means of the thromboplastin generation test revealed the lack of an essential factor not previously recognized. The name "Christmas disease" was used to describe this condition; the choice being directed by the name of the first patient investigated and the coincidental proximity of the 25th of December.[7] Christmas disease is clinically indistinguishable from hemophilia since it produces the same symptoms and has the same sex-linked type of inheritance. Like hemophilia, too, the clotting time is usually prolonged, the prothrombin time normal, and prothrombin consumption reduced. The thromboplastin generation test shows that antihemophilic globulin is normal in Christmas disease but that the serum lacks a factor (Christmas factor) which is normal in hemophilia. It is too soon to assess the incidence of Christmas disease, but from preliminary surveys it appears that one case might be expected to every ten of hemophilia. It is probable that "P.T.C. deficiency"[13] and "Haemophilia B"[11] are identical with Christmas disease. The relationship of P.T.A. deficiency[25] and factor 10 deficiency[16] is more problematic.

Factor 5 deficiency is a rarer condition than hemophilia or Christmas disease, and affects both sexes. The first case was described by Owren[26] under the name "Parahaemophilia." In this case the condition had existed from infancy, but there was no family history. In other cases,[9, 13, 29, 38] more than one member of the family was affected, the inheritance appearing to be non-sex-linked. The deficiency produces a prolongation of the clotting time and deficient prothrombin consumption and, in contrast to hemophilia and Christmas disease, prothrombin time is prolonged. Thromboplastin generation test shows an abnormality of the plasma component.

Factor 7 deficiency is also rare as a naturally occurring condition, although it is deliberately produced by the administration of the dicomarol drugs as a therapeutic measure in cases of incipient or established thrombosis. A few cases of congenital factor 7 deficiency (hypoproconvertinemia) have been described,[2, 30] and from a large family with twelve affected members studied by Owren,[29] it appears that the defect may be inherited as a simple dominant. In this condition, also, either sex may be affected and the prothrombin time is prolonged. The thromboplastin generation test locates the deficiency in the serum component, thus distinguishing the condition from factor 5 deficiency. The differentiation of these four thromboplastin-factor defects by means of their inheritance and the results of the prothrombin time and thromboplastin generation test is given in table II. It should be recognized that their occurrence in early childhood, even in absence of a family history, indicates the condition is probably hereditary and transmissible to future generations.

Rarest of all is congenital afibrinogenemia. In this condition there is complete, or almost complete, absence of fibrinogen from the blood giving rise to a hemophilia-like state. Some 11 cases have now been described,[8] either sex being affected and in four families there was consanguinity. It is therefore probable that the condition is inherited as a recessive character. The most striking abnormality is the incoagulability of the blood, even on the addition of brain extract or thrombin, and no fibrinogen can be detected by chemical methods. Despite the fact that no natural coagula-

tion of the blood is possible in these patients, most observers have remarked that the hemorrhagic symptoms are less severe than those of hemophilia.

TREATMENT

The rational aim of treatment in these conditions is the replacement of the deficient factors. Unfortunately, continuous prophylactic treatment, as in diabetes or pernicious anemia, is not possible because adequate amounts of effective preparations are not yet available. None of the many empirical remedies which have been recommended in the past has proved successful. In the present stage of therapeutic development, a temporary replacement only can be achieved by transfusing normal blood or by injecting certain plasma fractions containing the required factor.

In hemophilia blood transfusion has been much used in the past as a method for controlling hemorrhage. Any beneficial effects are presumably due to the presence in normal blood of the antihemophilic globulin, and preparations of this factor in a concentrated form have given good results. Unfortunately, the factor seems to have a variable stability, being present in certain blood samples but not in others. Therefore, it is necessary to transfuse blood as soon as possible after its withdrawal from the donor. Some of the disappointing results of transfusion or plasma-fraction therapy may be due to the use of inert material. An even more important point is now becoming apparent. Transfusions of as little as 50 ml. of plasma may reduce to normal the clotting time of a hemophilic patient's blood,[42] and it has been supposed that these small amounts should be effective in controlling bleeding. But such doses, though they may reduce the clotting time, do not correct the defective prothrombin consumption or thromboplastin generation of hemophilic blood.[4, 8] From experience of severe clinical hemophilia occurring in patients with normal clotting times, but defective thromboplastin generation, it is logical to suggest that therapy must render thromboplastin generation normal in order to be hemostatically effective. To achieve this a blood level of antihemophilic globulin of about 50 per cent normal is required, suggesting a minimum dosage of plasma or plasma fraction equivalent to half the normal blood content. Moreover such administrations must be repeated daily in order to maintain the effect. Such large doses have seldom been given in practice; the many failures reported may be due to inadequate therapy.

A serious complication of transfusion or antihemophilic globulin therapy is the development in certain patients of a refractory state in which there is no response to treatment. This failure to respond may be due to rapid destruction of the antihemophilic factor by the patient's blood, and in a few cases antibodies capable of inactivating the factor have been demonstrated.[14] Such an antigenic reaction, if it occurs, is an obvious stumbling block to therapy that must be surmounted or avoided if final success is to be achieved.

Factor 5 deficiency, like hemophilia, usually responds to large transfusions of normal blood or plasma, which should be as fresh as possible, since the factor rapidly disappears on storage. Factor 7 deficiency and Christmas disease can be treated with transfusions of fresh or stored blood or plasma, or even with serum, since the factors concerned are relatively stable and are not consumed during coagulation. It is

obvious that antihemophilic globulin will have no beneficial effect in cases of Christmas disease, thus emphasizing the necessity for identifying this condition.

Fibrinogen deficiency can be temporarily overcome by transfusions of blood or plasma or preparations of human fibrinogen. If the fibrinogen level of the circulating blood can be raised to 60 mg. per cent, clotting efficiency can be restored.[32, 37] Transfusions require to be repeated at 24 hour intervals in order to maintain the level.

Local treatment of wounds and other injuries, though often useful, cannot be relied upon to promote and maintain hemostasis in these hemorrhagic conditions. In all cases it is most important to avoid making local conditions worse by drastic attempts to control the bleeding. Ligatures, sutures, cauterization, and tight dressings are not only useless in these states, but they may be positively dangerous by promoting necrosis or extravasation of blood into the tissues. Therefore, local measures should be restricted to the application of some potent clotting factor together with an absorbable dressing such as fibrin foam, oxidized cellulose, or gelatin sponge. Thrombin is capable of coagulating the blood in all the conditions discussed with the exception of fibrinogen deficiency. Russell's viper venom will effectively coagulate the blood in cases of hemophilia and Christmas disease, but not in factor 5 deficiency, factor 7 deficiency, or fibrinopenia. The avoidance of trauma is naturally an important prophylactic measure. Even the most minor surgical procedures such as the extraction of a tooth or the incision of an abscess should not be carried out unless urgently required and can often be avoided by intelligent anticipation in conservative treatment. Major surgery should never be undertaken unless it provides the only hope of the patient's survival.

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The Diagnosis and Treatment of Hemophilia

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Hemophilia is an uncommon disease, but when one meets with such a condition in practice, it is absolutely necessary to understand all of the various factors involved. It follows Mendelian laws and is directly transmitted by daughters of hemophiliacs, who, while they are not hemophiliacs, will bear sons who are. There is statistical evidence that more males are born to such a family than females. Of these males, 89 per cent are hemophiliacs.

The disease is not usually manifest before one year of age and the only symptom is bleeding. Hemorrhage may occur spontaneously or follow slight trauma and may occur in any region of the body, the most frequent locations being the nose and mouth. Later a common bleeding point is into a joint. At the beginning this is absorbed, but in later life immobility often results.

Morphologically, the blood is normal except in cases of severe hemorrhage, where a secondary anemia may result. The only definite change is a marked prolongation of the coagulation time of venous and arterial blood. If any contamination of this blood occurs with tissue juices, the coagulation time will be considerably shortened giving a false sense of security. This shows that tissue fibrinogen is of great importance in the coagulation mechanism.

Probably nothing has caused so much discussion in recent years as the coagulation defect in hemophilia. The reader becomes confused with the variety and complex discussions of this phenomenon. Actually the difference of opinion is not as great as might be expected from the various theories given. Everyone agrees that there occurs a lack of available thromboplastin which is necessary to initiate the coagulation mechanism. However, the source and regulation of the catalytic agent that initiates the availability of the thromboplastin is the source of discussion.

The main source of thromboplastin in the blood is from the blood platelets. These are of normal value in the hemophiliac. However, Howell[1] observed that they failed to agglutinate readily *in vitro* and resisted disintegration. This has been shown to be true many times, and the postulation was therefore made that there was an inherent qualitative defect in the platelets of the hemophiliac. Brinkhous[2] found that there was a plasma factor that released thromboplastin from platelets, that was deficient in hemophiliacs, and Lewis[3] extracted a globulin from normal plasma that was capable of accelerating clot formation in the hemophiliac, that was not so active if the globulin was extracted from hemophiliac blood. Quick[4] believes that the failure of coagulation is due to a substance called thromboplastinogen which he states is congenitally and hereditarily deficient in the blood of the hemophiliac. This substance occurring in the plasma combines to thromboplastin by an

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activator derived from disintegrating platelets. Inasmuch as very little thromboplastin is formed, very little prothrombin will be activated to thrombin, and the coagulation complex will be incomplete.

To further complicate the matter, Tocantins[5] has found in several instances a circulating anticoagulant which is antithromboplastic in the blood of the hemophiliac. Ferguson[6] believes that the coagulation function is incomplete due to a deficiency in available trypsin.

These findings indicate that there is a general agreement on the failure of the blood to coagulate in the hemophiliac because of a failure of initiation of the first phase, namely, the conversion to thromboplastin. This reason, unless understood, will cause much confusion as the methods of treatment are founded on these various ideas. However, as none are entirely successful, the story is by no means completed, and much more work must be done to satisfactorily explain the phenomenon.

The diagnosis of hemophilia is made on the following criteria. (1) Family history. Theoretically there should be a history of abnormal bleeding in male members of the family on the mother's side. Actually, this may not be found as easily as one would think. In mild conditions any history may be lacking or inadequate. If it is found, it is of the greatest help in diagnosis. (2) Personal history. Here we should have a clear history of a deficiency in combating hemorrhage. While it may not be apparent until after the first year of life, there should be a clear history of hemorrhages from various parts of the body, including into the joints, that is uncontrolled. (3) Prolonged coagulation time of the venous blood (over 20 minutes) with a normal number of blood platelets.

Finally, there are a number of physiologic laboratory tests that vary in their importance but should be present. (a) Prolongation of the prothrombin consumption time or insufficient prothrombin consumption.[4] Inasmuch as there is a deficiency of thromboplastin, very little thrombin is formed in the presence of a normal quantity of prothrombin. The disadvantage of this test is that it is disturbed by all the anomalies affecting the first stage of coagulation and is therefore not specific for hemophilia. (b) Qualitative platelet defect.[7] If the blood is centrifuged and the coagulation time of the plasma estimated, a lengthened coagulation time with a normal platelet count, prothrombin time, and heparin titration is a qualitative platelet defect as is found in hemophilia. (c) Demonstration of a shortening of the coagulation time after the administration of antihemophiliac globulin. (d) Normal blood added to hemophiliac blood in small proportions shortens the coagulation time of the hemophiliac blood, whereas the addition of hemophiliac blood is ineffective.[8] (e) Soulier and Larrieu[9] recently announced a test for hemophilia in which other factors that disturb thromboplastin activity are eliminated. This is made by testing hemophiliac plasma freed from platelets and thromboplastin, with an extract of normal platelets deprived of antihemophilic activity.

The differential diagnosis must be made from other conditions that cause abnormal bleeding. These are leukemias, which have a rapid course, with fever, glandular enlargement, and enlarged liver and spleen. There is usually a marked anemia with a preponderance of abnormal or young white cells. A bone marrow examina-

tion will show a preponderance of one type of cell. Aplastic anemias will occasionally show abnormal bleeding from a lack of blood platelets. The peripheral blood will show an anemia much greater than is found in hemophilia, and the bone marrow will show hypoplasia of all elements. Acquired hemolytic anemia will frequently show abnormal bleeding as an early symptom. Here, however, the jaundice or increased blood bilirubin with the anemia that coexists is quite different from hemophilia.

Thrombocytopenic purpura frequently will show abnormal bleeding as an initial symptom. The diminution of blood platelets in the peripheral blood distinguishes the condition. Nonthrombocytopenic purpuras may cause difficulty, particularly rheumatic purpura or Schönlein's purpura, where bleeding into the joints is quite similar to hemophilia. There is no decrease in blood platelets or disturbance of thromboplastic action, and the coagulation time is normal. The same can be said for purpura abdominalis or Henoch's purpura where the bleeding is from the bowel. The coagulation time is normal, and there is frequently urticarial phenomenon.

The occasional instances of heparin increase, which cause faulty coagulation, can be distinguished by a heparin titration with protamine. If over 0.140 mg., this increase can be demonstrated, and a trial of protamine sulphate therapy, 400 mg. in 24 hours, will confirm the condition by its temporary correction.

Lastly, the rare condition parahemophilia[10] is a congenital hemorrhagic disease with deficient prothrombin activity by the one stage method corrected by the addition of prothrombin-free plasma. It shows a prolonged prothrombin time and a slightly prolonged coagulation time with a deficiency of Ac globulin. The "Christmas Factor,"[11] which is quite like hemophilia, is not reactivated by Cohn's fraction 1, but by normal plasma from which the antihemophiliac factor has been removed. This like the antihemophilic factor participates in thromboplastin formation.

Lastly, mechanical bleeding from the bowel may be mistaken for hemophilia, particularly if it is persistent and in small quantities over a long period of time. It may be enough to cause a low grade anemia quite like that found in hemophilia. This bleeding may be from polyps, a Meckel's diverticulum, ulcer, or from a chronic colitis. Here the coagulation time is normal, as well as other blood coagulation factors. The problem may be solved by study of the gastrointestinal tract with barium.

The treatment of hemophilia may be divided into two main groups, firstly, the control of acute hemorrhage, and, secondly, a long term course for the ultimate control of the condition. The problem in the first crisis is that of the control or therapy in maintaining a normal coagulation time for the duration of the emergency. The antihemophilic principle whatever it may be, as depending on the belief of the investigator, is present in whole blood or plasma. However, it must be fresh blood, and there is some evidence that it may vary from individual to individual. For this reason if results seem to be inadequate, different donors should be tried. In one hemophiliac under the author's care it was found that the blood best suited for this purpose was the father's.

A single venoclysis is generally sufficient, or at least all that is necessary for the coagulation time to remain normal for that individual, long enough for a coagulum

to form within the lumen of the hemorrhagic vessels. As a general rule, this is around 20 minutes actual coagulation time of arterial or venous blood. However, this may vary in individual cases. If the case has been studied long enough to establish the individual's base line for adequate coagulation, this value may be considered satisfactory. If much blood has been lost, fresh whole blood should always be used since it provides red blood cells besides the hemophilic substances.

However, the use of fresh whole blood or plasma is hampered by the fact that it is not always readily available. The antihemophilic principle may be prepared from nonhemophilic blood by freezing or lyophilizing plasma within a few hours of withdrawal from a donor. This activity deteriorates rapidly under most *in vitro* conditions. In the restoration of frozen plasma, a rapid thawing in a water bath at 37 C. must be done, otherwise the plasma proteins will denature with precipitate formation. Both properly prepared frozen or lyophilized plasma provide an excellent permanent readily available source of antihemophilic substance.

The concentrated unit of powdered plasma, Fraction 1 of Cohn, is reliquified with distilled water and has a protein equivalent of 60 to 75 cc. of plasma with an antihemophilic activity of 10 to 15 times the comparable volume of plasma from fresh blood. Intravenous administration is more reliable in reducing the coagulation time than intramuscular injection. Fifty cc. of fresh restored frozen or lyophilized plasma intravenously will maintain the coagulation time in a moderately severe hemophiliac condition for 24 hours. One unit of Cohn's plasma Fraction 1 (equivalent to 0.2 Gm. of protein) will do the same, but its action is variable from three hours to 65 hours.

For the past five years, the author has been using another approach to the treatment of hemophilia. The reasons for this are that reactions may occur with fresh blood, which may not always be available, and the author's results with frozen plasma or dried fractions have not been entirely satisfactory. The other approach is the use of histamine.

Its use is based on the clinical and experimental evidence that intravenous or subcutaneous injections of histamine increase directly the qualitative disintegrative ability of the blood platelets.[12] This may be due to an antagonistic action between heparin and histamine. Heparin in high concentrations does not inhibit completely the increased tendency toward *in vitro* agglutination of the platelets exposed *in vivo* to histamine.

The following plan was followed: histamine 0.1 mg. is given the first day, 0.2 mg. the second, 0.4 mg. the third, 0.8 mg. the fourth, and 1.0 mg. the fifth. If given intravenously, the histamine is given in 250 cc. of isotonic sodium chloride solution at a rate of 20 drops per minute. By hyperdomoclysis, the same quantity is given at the rate of 10 drops per minute. This has shortened the time of a bleeding cycle and increased the time between cycles in a majority of instances.

In almost all patients, there is a tendency for the condition to become more refractory as the treatments are continued. In these individuals, it is better to give the treatment between bleeding cycles and extend the course several injections. However, the quantity of histamine should never be over 1.0 mg. even in a longer

series. The action of histamine is not permanent and may fail utterly in some cases, but the author has found it to be of value in the majority of instances.

In some instances, where a hemophiliac has received many transfusions of blood or plasma, there is also a lessening of the usual effect of these agents. Monroe[13] thought that this might be due to anticoagulant that was formed. This may actually be an antibody which inhibits the antihemophilic globulin. Van Crevald[14] has given ACTH and Cortisone to a hemophiliac who experienced such a reaction with beneficial results, which offers clinical proof that the action is an antibody-antigen reaction.

It is most important to have the hemophiliac in condition for the occasional surgical operation that may be necessary. It is not true that the hemophiliac cannot be safely operated upon. In an emergency, a transfusion of whole blood or plasma will hold the coagulation time to a safe proportion. The only bleeding will be from small arterioles anyway, and with a base line of 20 minutes, no danger will be forthcoming. In an operation that is not an emergency, or in tooth extraction, for most hemophiliacs have bad teeth, the time of a-period-between coagulation cycles can be determined and the individual operated upon at that time. The child or adult should be hospitalized for a time before the operation, and the blood coagulation estimated several times a day. Whatever form of therapy is decided on can be used, and if successful in keeping the blood coagulation down, operation may be performed. In the postoperative period, the blood should be studied similarly and therapy continued for six to ten days as the case may require.

Local hemostatic agents used at the site of hemorrhage are not successful. Of the multitude of forms of therapy that have been suggested, only fibrin foam, thrombin mixtures, and local pressure have been at all successful. Other methods have a doubtful value, if any.

The second important point in the treatment of the hemophiliac is a long term course for the ultimate control of the condition. This should begin as soon as the diagnosis has been proved by training the child in early life to adapt himself and to accept various limitations enforced by the illness. While it is quite true that most of these instances are observed in childhood, the disease is no worse in childhood than at a later period in life. It is only that most physical hyperactivity and immaturity of perception make the child more susceptible to incidental and accidental trauma with the initiation of hemorrhage.

The cooperation of the physician in explaining the condition to the parents with its attendant limitations of activities, that endanger the child with the possibility of resulting injuries, is extremely essential. The finest tact is necessary to keep the child from becoming a psychologic cripple. Not only should the physician and parents cooperate in this, but the medical social worker and school authorities can all help in outlining a satisfactory conduct of restricted activity. It is only by this means that there can be developed a normal childhood that will avoid the occurrence of hemorrhagic episodes which might well develop into an invalid personality.

Finally, one must not overlook proper help and progress with the physical

therapist and orthopedist. Such necessary care that they might outline will often arrest what otherwise might be a permanent crippling disability. Sooner or later, hemorrhage into the joints will result, and it is here that these specialists can be of such material benefit.

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Neonatal Thrombocytopenia*

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The hemostatic mechanism of the newborn infant is in a state of potential insufficiency. The capillary vessel is very fragile, and the coagulation process is impaired because the concentration of plasma stable factor[1] or prothrombinogen[2] is often reduced. Also, there is often some reduction in the platelet count.[3] Clinical bleeding is, nevertheless, rare unless the platelet count is markedly depressed. When this occurs, at birth or shortly after birth (one–two weeks) severe bleeding manifestations may follow. Neonatal thrombocytopenia has recently aroused a good deal of interest in view of its important etiologic and therapeutic implications. These will be discussed in the present short review of the subject.

Neonatal thrombocytopenia is a complex syndrome rather than a definite entity. Clinical and etiologic classifications, based on the authors' experience, are presented in tables I and II respectively. Both emphasize the multiplicity of etiologic causes and indicate why the elucidation of a case of neonatal thrombocytopenic purpura may require, in addition to the routine clinical examination and laboratory tests, careful study of the peripheral blood smear and of the tibial bone marrow as well as the use of many specialized technics of relatively recent introduction (search for platelet agglutinins in the patient's plasma, determination of the patient's platelet group and type, et cetera). In fact, the study of neonatal thrombocytopenia is as involved as that of the thrombocytopenic states in the adult and may be modeled after it.

Neonatal thrombocytopenic purpura rarely is seen as the presenting symptom in septicemia and in congenital syphilis, et cetera. Its pathogenetic mechanism in these conditions is not clear. Thrombocytopenia is a constant feature of congenital acute leukemia, which, in the newborn, is extremely rare. Only about twenty-two authentic cases have been described thus far.[4, 5] It is almost always of the granulocytic variety and very seldomly of the lymphocytic variety.[6, 7] The thrombocytopenia, as always in leukemia, follows failure of platelet production due to replacement of the bone marrow megakaryocytes. Congenital developmental abnormalities are often present along with acute leukemia.[4]

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TABLE I

Neonatal Thrombocytopenia: A Clinical Classification

(a) Secondary to	1. Sepsis, et cetera.	
	2. Congenital syphilis.	
	3. Acute congenital leukemia.	
	4. Erythroblastosis fetalis.	
(b) Idiopathic	1. Amegakaryocytic—	Fanconi's syndrome (when this is present at or shortly after birth).*
		Congenital hypoplastic thrombocytopenia (megakaryocytic hypoplasia).
	2. Megakaryocytic—	Infants of normal mothers
		A. Acute and chronic idiopathic thrombocytopenic purpura.
		B. Immunologic (platelet incompatibility between mother and fetus).
		Infants of thrombocytopenic mothers
		A. Immunologic (transplacental passage of platelet agglutinins)†.

* Perhaps, an incomplete variety of the Fanconi's syndrome. As in the Fanconi's syndrome, other congenital malformations are present.

† Thrombocytopenia may be caused in the newborn by the passage through the placenta of an offending drug and of a plasma factor from the sensitized mother to the fetus.

TABLE II

Neonatal Thrombocytopenia: An Etiologic Classification

(a) *Failure to platelet production*
1. Acute congenital leukemia.
2. Sepsis, etc. (?)
3. Congenital syphilis (?)
4. Fanconi's syndrome.
5. Congenital hypoplastic thrombocytopenia (megakaryocytic hypoplasia).

(b) *Excessive peripheral destruction of platelets* (immunologic mechanisms ?)

1. Erythroblastosis fetalis { with detectable platelet agglutinins. / without detectable platelet agglutinins.
2. Idiopathic thrombocytopenic purpura { acute variety. / chronic variety.
3. Transplacental transfer of platelet agglutinins (or lysins ?) from thrombocytopenic mothers.
4. Drug thrombocytopenia (transfer through the placenta of a platelet destructive factor and of the offending drug).
5. Platelet type incompatibility between mother and fetus.

Severe cases of erythroblastosis foetalis are often accompanied by thrombocytopenic purpura.[8] Purpura is rapidly controlled by the administration of ACTH, 10 to 15 units daily, and of cortisone, 15 to 25 mg. daily, although thrombocytopenia may not be as easily controllable. Exchange transfusion, if successful, causes prompt rise in the platelet count. The pathogenetic mechanism of the thrombocytopenia is almost certainly immunologic. It appears as if the destructive process involving the red cells may attack platelets as well. In rare cases, the immunologic mechanism may be demonstrated with the detection of platelet agglutinins in the plasma of the

patient (figure 1). The mechanism of the thrombocytopenia in these cases is perhaps similar to that described for idiopathic thrombocytopenic purpura of the chronic variety, where circulating platelet agglutinins may be demonstrated.[9, 10] The association of hemolytic anemia and thrombocytopenia is also comparable in many aspects to the combined syndrome of acquired hemolytic anemia and thrombocytopenic purpura described by Evans et al.[11] In a number of Evans' cases, agglutinins against platelets as well as against red blood cells could be demonstrated.

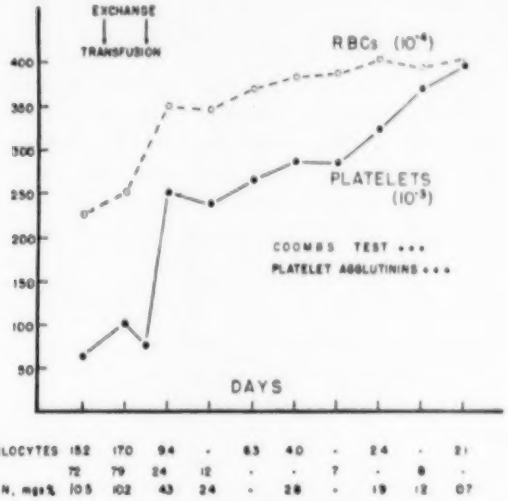

FIG. 1. Associated Erythroblastosis and Neonatal Thrombocytopenia, with Demonstrable Platelet Agglutinins in the Patient's Plasma.

Two exchange transfusions, at 30 hours interval, caused prompt improvement in the thrombocytopenia of the infant and disappearance of the clinical purpura.

Thrombocytopenia is one of the symptoms of familial or of sporadic Fanconi's syndrome (congenital hypoplastic anemia with multiple congenital malformations). In a limited number of cases, the syndrome may be fully developed at birth or shortly after birth. In other instances, the bone marrow hypoplasia may be limited to the megakaryocytes, thus the patient presents thrombocytopenia but not anemia or leucopenia.[12, 13, 14] The pathogenetic mechanism of the megakaryocytic hypoplasia completely escapes us at the present time. The authors recently studied in detail a case of this condition which they propose to call, along with Akerrén and Reinand,[14] congenital hypoplastic thrombocytopenia. In this particular patient, there were purpura, thrombocytopenia due to striking reduction of the number of bone marrow megakaryocytes and multiple congenital anomalies (absence of radii, dislocation of hips, et cetera).[15] The bleeding tendency of the patient was improved by splenectomy, but the platelet level rose to subnormal levels only. Possibly, this

type of neonatal thrombocytopenia often goes undiagnosed, especially since its detection depends on the availability of a good and representative bone marrow specimen. In fact, in the authors' experience, any thrombocytopenia present at birth or early in the neonatal period which persists after the first year of life should be considered due to bone marrow failure, if no platelet destructive mechanisms (agglutinins) can be demonstrated in the patient's plasma. Congenital anomalies need not be present, and a good bone marrow sample should always be obtained in these cases.

Another more commonly encountered group of neonatal thrombocytopenias includes cases which are a more fitting counterpart of idiopathic thrombocytopenic purpura in adults. Platelets are decreased in the peripheral blood, but the bone marrow presents normal or increased number of megakaryocytes, perhaps with evidence of decreased platelet production. These patients may be further divided into two groups: (a) those with normal mother; (b) those with thrombocytopenic mother. When the mother is normal, a thrombocytopenic child may have conceivably developed idiopathic thrombocytopenic purpura of the acute or chronic variety as a response to infectious or allergic stimuli during the intrauterine life. Such cases, if they exist at all, must be extremely rare. Or thrombocytopenia may be present at birth and perhaps due, as postulated recently,[10] to platelet type incompatibility between mother and fetus. There is fairly general agreement that platelets are antigenic, and work based on this concept has brought forth the discovery that different platelet groups and types exist.[10, 16] The mechanism through which platelet incompatibility causes thrombocytopenia in the newborn should be similar to that operating in erythroblastosis fetalis. A case of this type of neonatal thrombocytopenia is presented schematically in figure 2, where the characteristic laboratory findings of this syndrome are also summarized.

If the mother suffers from chronic idiopathic thrombocytopenic purpura, thrombocytopenia in the infant is probably due to the transmission of a platelet offending agent from the maternal to the fetal circulation.[17] Thrombocytopenia in the mother need not be present at the time of examination but might have improved or altogether remitted following splenectomy. The responsible factor is apparently not of splenic origin, since thrombocytopenia may be found in a newborn infant, although the mother has been recently splenectomized. It is probably a circulating platelet agglutinin, such as have been found in about 50 per cent of the patients with idiopathic thrombocytopenic purpura of the chronic variety. We know that the agglutinin may cause all features of the disease, peripheral thrombocytopenia, characteristic changes in the bone marrow megakaryocytes included.[9] The agglutinin may persist even after splenectomy[18, 19] and its passage through the placenta could determine all features of the disease in the fetus and the newly born. Miscarriage or neonatal purpura follow. There is apparently a direct relation between ability of the mother to cause thrombocytopenia in the infant and presence of platelet agglutinins in her plasma. Thus, in the authors' experience, the plasma of mothers of two infants born with thrombocy- penic purpura contained platelet agglutinin. Also, the authors' experience shows that no thrombocytopenia develops in the newborn infant when the mother's plasma does not contain platelet agglutinins. The authors

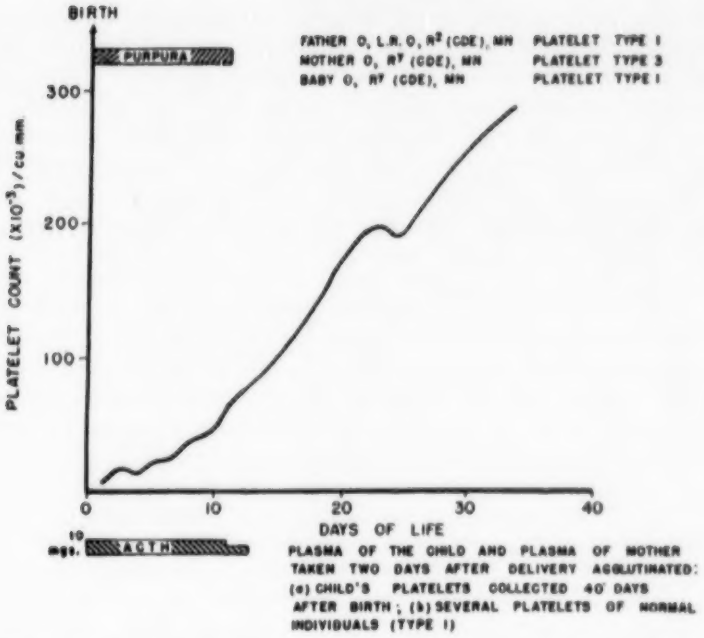
BIRTH
PURPURA
FATHER O, L.R. O, R² (CDE), MN PLATELET TYPE 1
MOTHER O, R² (CDE), MN PLATELET TYPE 3
BABY O, R² (CDE), MN PLATELET TYPE 1
300
200
100
PLATELET COUNT (X10⁻³)/cu mm.
0
10
20
30
40
DAYS OF LIFE
19 mgs.
ACTH
PLASMA OF THE CHILD AND PLASMA OF MOTHER TAKEN TWO DAYS AFTER DELIVERY AGGLUTINATED: (a) CHILD'S PLATELETS COLLECTED 40 DAYS AFTER BIRTH; (b) SEVERAL PLATELETS OF NORMAL INDIVIDUALS (TYPE 1)

FIG. 2. Neonatal Thrombocytopenia Due to Mother-Fetus Platelet Type Incompatibility. Mother was normal. The patient, the third child, was born with severe thrombocytopenic purpura. Purpura was controlled promptly by ACTH, and the platelet count began to rise shortly after that. Immunologic studies revealed the following facts: (a) mother's platelet type was 3 (no agglutinogens); that of father's and child's platelets, 1; (b) mother's plasma and child's plasma collected at birth (and frozen) agglutinated father's platelets, child's platelets collected 40 days after delivery, and platelets from some individuals on type 1; (c) the platelet agglutinin disappeared from the plasma of mother and child 60 days after delivery. Unfortunately, the patient's siblings were not available for examinations and studies. They were born normal. Passage of platelets type 1 or platelet products into mother of platelet type 3, apparently caused production by the mother of anti-1 type platelet agglutinin. In turn, passage of this agglutinin from the maternal to the fetal circulation induced thrombocytopenia in the fetus and its presence at birth.

verified this in three cases which came to their attention. Finally, it is generally admitted that amegakaryocytic (leukemia, aplastic anemia) and hypersplenic types of thrombocytopenia in the mother are not accompanied by neonatal thrombocytopenia. This problem, as outlined here, is of great practical importance and should receive further attention. It seems logical to conclude on the basis of the available evidence that children of a mother whose plasma contains platelet agglutinins are good candidates for neonatal thrombocytopenia.

There is, finally, another variety of neonatal thrombocytopenia, caused by drug sensitivity in the mother. This type is extremely rare, only one fairly well-authenticated case having been reported thus far.[19] In this instance, a quinine-sensitized

mother received the drug at the time of delivery. She promptly developed thrombocytopenia and a purpuric infant was born. We know from Grandjean[20] and Ackroyd[21] that drug thrombocytopenia is due to the activity of a plasmatic factor which has developed in a sensitized patient and is able to agglutinate or lyse platelets in the presence of the offending drug. Both the latter and the plasma factor must have passed the placental barrier in Posner's case,[19] thus causing thrombocytopenia in the infant.

All types of megakaryocytic idiopathic neonatal thrombocytopenia present certain common characteristics. Splenectomy in the mother does not prevent but greatly reduces the severity of the thrombocytopenia in the newborn. Thus, it should be carried out in every pregnant woman with idiopathic thrombocytopenic purpura, preferably prior to the fifth month of pregnancy. In the infant, thrombocytopenia and purpura are self-limited, seldom severe enough to require blood transfusions and quickly controlled by the use of ACTH and cortisone. Cases due to transplacentar transfer of platelet agglutinin raise important questions. The authors' studies in idiopathic thrombocytopenic purpura of the adult indicate that thrombocytopenia persists as long as the platelet agglutinin is present. The survival time of an injected platelet agglutinin is from 12 to 14 days.[9] Like the red cell agglutinin in erythroblastosis fetalis, however, the platelet agglutinin causing thrombocytopenia in the newborn infant may remain in the circulation for as long as 3 to 4 months. It is felt,[8] therefore, that thrombocytopenia persisting 6 to 12 months after delivery is more likely due to megakaryocytic hypoplasia (as previously mentioned) or to the development (and not the transfer) of an immunologic mechanism against platelets. Studies of the morphology and function of the bone marrow megakaryocytes and of the ability of the patient's plasma to agglutinate (or, perhaps, lyse) platelets will, in the future, help greatly in the pathogenetic interpretation of these cases.

SUMMARY

1. Neonatal thrombocytopenia is a complex syndrome which may be due to several pathogenetic mechanisms: one group of cases is due to insufficient platelet production (congenital hypoplastic thrombocytopenia or megakaryocytic hypoplasia, congenital acute leukemia, perhaps sepsis, etc.); another to excessive destruction of platelets at the periphery and, perhaps, inhibition of megakaryocytic activity as well (erythroblastosis fetalis, transplacental transfer of platelet agglutinin from mother to fetus and development of an agglutinin in the mother against the child's platelets due to platelet type incompatibility).

2. Of the first group, acute leukemia has unfavorable prognosis; hypoplasia of the bone marrow megakaryocytes (whichever the cause might be) may be helped by splenectomy. The second group includes self-limited cases where administration of ACTH or cortisone may decrease the purpura while one waits for spontaneous recovery, which occurs in practically every case.

3. Splenectomy in the mother reduces the severity of neonatal thrombocytopenia due to placental transfer of platelet agglutinins, but does not prevent it.

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Idiopathic Thrombocytopenic Purpura in Childhood

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Purpura in childhood is usually symptomatic, associated with infections, with the rheumatic process, or with toxic states. Cases of the essential or idiopathic variety of thrombocytopenic purpura (I.T.P.) do occur, however, and the recognition and management of such cases is of importance. I.T.P. may be defined as a hemorrhagic state, mainly affecting females, arising without known etiologic cause and characterized by thrombocytopenia, capillary fragility and normal or increased numbers of megakaryocytes in the bone marrow. The disease is very rare in infancy.[1, 2] Many of the recorded cases have been babies whose mothers were suffering from thrombocytopenic purpura. In these circumstances, the condition is evident at birth, and the course is usually mild. This condition is possibly due to the transplacental passage of the factor responsible for the thrombocytopenia in the mother.[3] In childhood, however, there is a high incidence of I.T.P.; in fact, the disease manifests itself before the age of 12 in about 50 per cent of cases.[4]

ETIOLOGY

The etiology remains obscure, but recent work tends to suggest that a number of different etiologic agencies may be implicated in this syndrome. Abnormal activity of the spleen and reticuloendothelial system has long been suspected, resulting either in excessive destruction of platelets[5] or overproduction of some humoral factor which inhibits platelet release from the bone marrow.[6, 7] Circulating factors producing agglutination and lysis of platelets have recently been demonstrated in some cases.[3, 8] These developments may lead to a differentiation of groups within the syndrome of I.T.P. which will enable treatment to be more specific.

COURSE

The course of this disease has been well described and needs little elaboration. It should be remembered that the condition is naturally remittent, especially in childhood. In the writer's experience, the danger to life from I.T.P. increases with age, and conservative treatment can therefore be considered more freely in young patients. Commonly, incidents are few and widely spaced in childhood and serious difficulties only arise after puberty with the onset of menstruation.

DIAGNOSIS

The diagnosis of this idiopathic variety of thrombocytopenic purpura in childhood presents difficulties. Reviewing 56 cases of purpura in childhood, personally observed, the writer finds that in 32 cases the condition was closely related to an acute infection, commonly streptococcal. Of these cases, 23 were thrombocytopenic

and the remaining 9 showed vascular fragility only. The majority of these post-infective states resolved spontaneously. Of the 24 cases without preceding infection, 17 were ultimately classified as I.T.P. on the grounds that no etiologic factor could be incriminated and all other diagnostic criteria were satisfied. These criteria are as follows. Thrombocytopenia is constant, usually of the order of 10,000 to 50,000 per c.ml. The blood shows no other cytologic abnormality apart from any changes due to blood loss. Clot retraction is impaired. Prothrombin consumption is subnormal. The bleeding time is prolonged. Capillary fragility is usually marked, whether measured by positive pressure (Hess test) or negative pressure methods. Bone marrow examination is essential, in order to demonstrate that megakaryocytes are present in normal or increased numbers. Careful study of these megakaryocytes will reveal a lack of platelet production.

TREATMENT

Many measures have been advocated in the treatment of I.T.P., but at the present time there are three procedures which hold out reasonable hope of success: blood transfusion, ACTH or cortisone therapy, and splenectomy. As indicated earlier, there is good reason to expect subsidence of acute episodes in childhood, and, therefore, conservative treatment should always be applied and surgical intervention avoided unless good indications are present.

Blood transfusion is a measure of definite, though transitory value. In addition to the replacement of lost blood, transfusion has two theoretical advantages. If fresh blood is used, platelets are supplied. Many observers, however, have failed to demonstrate any significant increase in number of circulating platelets after transfusion. This may, however, be simply a matter of the range of error in the counting method since, if concentrated suspensions of platelets are infused, a distinct numerical increase can be found. In some cases a very rapid disappearance of transfused platelets is noted and this may be due to the presence of platelet agglutinins.[3] A second effect of transfusion is on the capillaries. A definite increase in capillary resistance results from transfusion of whole blood in many cases of I.T.P., and this can occur quite independently of any change in circulating platelet levels. In the author's opinion, the beneficial effects of transfusion of whole blood are usually due to this improvement in capillary state. Blood transfusion is therefore the mainstay of conservative treatment and should be repeated as necessary to tide over the acute phase.

The effects of ACTH and cortisone in I.T.P. have been described by a number of authors.[9, 10, 11, 12] The results are variable, and range from no effect to full remission. The author's experience, using these substances in 12 cases in children, has been that in 4 cases there was no beneficial effect whatever. In the remaining 8 cases there was clinical improvement of varying degree. Six of these showed improvement in capillary state only without significant change in platelet levels. Remission in these cases tended to be short-lived. Similar experience has been reported elsewhere.[13] In 2 cases only a sustained increase in platelets followed the administration of ACTH, and in both cases prolonged remission resulted. It

has been suggested that ACTH and cortisone achieve their effect by the suppression of platelet agglutinin,[3] and this may be one mechanism while an effect on the capillaries is another.[14] These substances are certainly worthy of trial in any severe case of I.T.P.

Splenectomy is well-established as a remedial measure in I.T.P. The operation should only be undertaken in children when very definite indications exist. The diagnosis must be firm and the marrow must have an adequate megakaryocyte content. Conservative measures should be given a thorough trial. If no remission is forthcoming after a period of weeks, then the operation may be considered. The main indication for immediate splenectomy is the development of any sign of hemorrhage in the central nervous system. This is fortunately very rare in children. Failure to respond to ACTH or cortisone is no contraindication to splenectomy; in fact, it is the author's growing impression that those cases which fail completely on ACTH or cortisone frequently show the optimum response to splenectomy.

I.T.P. is thus a disease which the pediatrician probably encounters more frequently than the general physician. It seems increasingly likely that it is not a single disease state, but is a syndrome produced by several different etiologic mechanisms. It is to be hoped that the elucidation of these will lead to more specific and accurate treatment of any individual case.

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The Dynamic Concept of Hemofluidity

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It has been long recognized that thrombin is elaborated from prothrombin, its inactive precursor, and that the conversion is enhanced by calcium ions and thromboplastin. The existence of accelerator factors and inhibitors has recently been postulated, if not recognized as fact, and will be discussed. This general phase, proceeding toward the elaboration of thrombin, is identified as the conversion phase, or first stage, of the clotting mechanism. It is followed by the clotting phase or second stage, the production of the fibrin clot, which accomplishes physiologic hemostasis. Either of these stages may be inhibited by heparin.

As short a time as five years ago, this was the scheme presented. During this last interval an entirely new concept has demanded elaboration even though hinted at as far back as 1875. The lytic phase of the coagulation mechanism is referred to here. This area may also be bisected into two stages. The first of these is the conversion phase, the production of the active enzyme fibrinolysin, and the second the solution of the fibrin clot. This lytic phase has its kinases, inhibitors, and undoubtedly its accelerators. Thus, the close resemblance of the "solution" stage to the "gel" stage in the problem of hemofluidity becomes apparent.

Because of the complexity of the reactions and interactions of the proteins and lipoproteins involved in maintaining the equilibrium under discussion, it is logical to discuss briefly the components and then the reactions involved in the formation of the dynamic equilibrium in circulating blood.

CLOTTING REACTANTS

1. *Prothrombin and Thrombin:* High yields of the most stable thrombin preparations are obtained by the method of Seegers et al.[1, 2] In this method the purified prothrombin is converted to thrombin by the addition of beef lung thromboplastin and ionic calcium. Recently, Seegers[3] reported that purified prothrombin in 25 per cent sodium citrate solution is slowly converted to thrombin. A number of articles have appeared on the stability of prothrombin indicating that if properly stored it remains quite stable. Normal plasma contains less than 0.2 mg. per ml. The isolated protein is a white amorphous powder containing tyrosine, carbohydrate, glucosamine, tryptophane, and 14.5 per cent nitrogen.[4] Of importance in this discussion is that Carter et al[5] in their physiologic studies found no evidence of a reserve supply of prothrombin outside the circulating blood. Mann et al[6] present evidence for a rapid destruction and replacement of prothrombin and other related proteins.

2. *Thromboplastin and Platelets:* Lung and brain yield the most potent preparations of thromboplastin, though all secretions and tissues possess activity. Products

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from these two sources differ in their contamination with accelerator globulin. Brain contains little, while the lung thromboplastin contains considerable quantities even after several $(NH_4)_2SO_4$ purification fractionations. Ultracentrifugal sedimentation reduces the contamination still further and Chargaff's technics[7] yield a lung preparation relatively free from accelerator globulin. It is this accelerator contamination, however, which makes the lung thromboplastin a suitable reagent for the two stage prothrombin assay. The brain product may be made into a satisfactory reagent for this determination by the addition of purified accelerator globulin.

It has not been proved whether thromboplastin acts on prothrombin catalytically or if the reaction is stoichiometric. In 1939 Mertz et al[14] reported the latter. Owren[15] showed that the limiting factor is accelerator globulin rather than thromboplastin. Seegers[3] now agrees with Owren and presents the observation that prothrombin can be converted to thrombin in the absence of thromboplastin.

Platelets, whether they contain thromboplastin,[8] prothrombin conversion factor,[9, 10] Ware's thrombin-fibrinogen factor,[11] or only the vasoconstrictor substance of Zucker,[12] are also important in the clotting of blood as evidenced by the alteration of prothrombin utilization studies of Buckwalter et al.[13]

3. *Fibrinogen and Fibrin:* Fibrinogen was one of the first coagulation proteins to be purified chemically. It can be prepared by alcohol fractionation,[16] salt fractionation procedures, and the freezing-thawing method of Ware et al.[17] In the latter method, no chemicals other than anticoagulant and physiologic saline need come in contact with the fibrinogen. Laki[18] reported crystalline porcine fibrinogen in the form of small monoclinic needles which tend to form star shaped patterns. Block and Bolling[19] and Brand et al[20] have reported rather extensively on the composition of fibrinogen and fibrin. Fibrinogen is a very large asymmetric molecule making a viscous solution. Its isoelectric point is 5.5 in a 0.1 ionic strength solution. Fibrinogen and fibrin are important because they are the substrate proteins in the enzyme reactions under discussion. Thrombin converts fibrinogen to fibrin, splitting off the fibrinopeptide of Lorand.[21] That fibrin is then dissolved by thrombin has been confirmed by Guest and Ware.[22] Fibrinogen and fibrin are digested by fibrinolysin at approximately the same rate and yield very similar degradation products, several of which have been isolated.[23]

An additional property of purified fibrin clots is high tensile strength. This makes fibrinogen and thrombin of special importance in such surgical procedures as skin grafting and removal of renal calculi.

4. *Accelerator Globulin:* Discussion under this heading will be brief, since little is known about this class of substances. Owren[15] showed that accelerator globulin (factor V in his nomenclature) is a globulin, thermolabile at 58 C. for 30 minutes and nondialyzable through a cellophane membrane. Its minimum solubility is in the range of 33 to 50 per cent saturation with $(NH_4)_2SO_4$ and the isoelectric point lies between *p*H 5.0 and 5.5. All coagulationists agree that accelerator globulin acts in the first stage of clotting by aiding the conversion of prothrombin to thrombin. There is much disagreement as to whether it acts catalytically or stoichiometrically.

Owren[15] was the first to postulate the stoichiometric reaction. He believes that accelerator globulin rather than thromboplastin is consumed during the reaction.

Lewis and Ferguson,[24] working with highly purified reagents, reported that the thrombin yield is dependent upon the amount of thromboplastin and accelerator globulin present. If accelerator globulin acted catalytically, one would expect the rate but not the total globulin yield to be affected.

Quick and Stefanini[25, 26] also agree with the stoichiometric principle. They claim that in accelerator globulin-deficient plasma very little prothrombin is utilized during the clotting reaction. Even the addition of excess ionic calcium and thromboplastin only slightly increases the prothrombin consumption in such plasma. Alexander et al[27, 28] emphasize the fact that the accelerator globulin content of serum is lower than that of plasma. Serum prepared from hypoprothrombinemic plasma is richer in accelerator globulin than is normal serum. These observations would seem to indicate that the accelerator is used up in the conversion reaction.

Seegers[3] and McClaughry and Seegers[29] claim that accelerator globulin, thromboplastin, and ionic calcium are all unnecessary for the *in vitro* conversion of prothrombin to thrombin. They observe that purified prothrombin dissolved in 0.72 *M* sodium citrate is activated to thrombin. This is strong evidence for the catalytic hypothesis, if the prothrombin used in these experiments is absolutely free of other reagents. Also pointing in this direction is the observation of Flynn and Standley[30] that when blood clots in the presence of an equal volume of 0.11 *M* $CaCl_2$ no detectible quantity of accelerator globulin is consumed.

It might be concluded that accessory factors, here typified by accelerator globulin, are required for physiologic hemostasis.

5. *Activators of Profibrinolysin:* Initially, profibrinolysin was activated by chloroform, and Tagnon[31] published an excellent report on the activation in plasma and serum. Such other chemicals as acetone, alcohol, potassium cyanide, and sodium citrate produce lesser activation.[32]

Christensen[33] was the first to recognize streptokinase activation of profibrinolysin, and he has worked extensively on the purification and isolation of this bacterial exotoxin. Streptokinase is not precipitated by protamine between *p*H 5 and 6.5 and thus affords an excellent means of removing a large part of the broth contaminants, conjugated nucleic acids. Streptokinase undergoes reversible inactivation with changes in *p*H. It is heat labile.

Staphylokinase of Gerheim[34] is another activator of certain profibrinolysins. It contains a proinhibitor which under certain conditions interferes with its activity. Since profibrinolysins of different species are more readily activated by specific kinases,[32, 34] caution must be employed in studies in this field.

Fibrinolysokinases of tissue origin (cyto-) and urinary origin (uro-) also appear in the literature. Astrup[35, 36, 37] has reported on both types of activators. The urokinase is quite unstable and relatively difficult to concentrate. Guest,[38] however, has evolved a workable procedure which may supply adequate quantities of this product. The insolubility of the tissue kinases is impeding progress toward their purification and use.

6. *Profibrinolysin and Fibrinolysin:* Profibrinolysin, the inactive precursor of fibrinolysin, is found in the globulin portion of plasma. It is water insoluble, is precipitated by acidification to *p*H 5.5, and is best concentrated in the 25 to 30 per

cent saturated $(NH_4)_2SO_4$ fraction from serum.[39] The profibrinolysin of each species is activated best by its specific activator or kinase.[32] *In vivo* profibrinolysin may become activated as part of the "alarm reaction" through Ungar's pituitary-adrenocortical-spleen mechanism.[40]

The active enzyme, fibrinolysin, is an euglobulin with its isoelectric point at about *p*H 5.5. It is relatively unstable in solution at 26 C., showing about 40 per cent loss of activity in 8 hours. The lyophilized enzyme is much more stable.[32] In the coagulation mechanism, fibrinolysin digests prothrombin, fibrinogen, and fibrin. It does not inactivate thrombin or thromboplastin. It combines with antifibrinolysin from the albumin portion of plasma to yield an inert protein possessing neither lytic nor antilytic properties. It has been possible to reactivate the fibrinolysin from certain of these neutral compounds.

INHIBITORS

7. *Antifibrinolysin:* Antifibrinolysin is a protein obtained from the albumin fraction of blood plasma. This antienzyme blocks the action of fibrinolysin on fibrin, fibrinogen, and prothrombin. It is prepared by a combination of salting out and isoelectric precipitation technics and can be obtained readily about 80 per cent pure.

Extensive experiments[41] performed in purified clotting systems show that antifibrinolysin is not an antithrombin, antiprothrombin, or antithromboplastin and that it does not affect the activity of accelerator globulin or the clottability of fibrinogen. These findings are not accepted by some investigators; during a discussion period at the Josiah Macy Conference,[32] it was noted that conflicting results have been obtained when similar but not identical reagents are used.

8. *Antithrombin:* When whole blood clots, the formed thrombin rapidly disappears, being inactivated by at least two mechanisms. The first is the adsorption of thrombin on the formed fibrin; the second is the inactivation of thrombin by antithrombin. Plasma contains active antithrombin and a reserve store of proantithrombin which is activated by heparin.[42] In our laboratory we have recently isolated proantithrombin,[43] substantiating this idea. An anomaly which we observed was the variation in potency of different lots of purified proantithrombin that may be due to the amount of lipid present. Support for this hypothesis is the work of Snellman et al[44] who have isolated a heparin-polypeptide-lipid residue from mast cell cytoplasm. The polypeptide has a molecular weight of about 8,000; the lipid contains lecithin, cholesterol, and neutral fat. Native heparin is loosely combined with this lipoprotein. Neither segment possesses activity per se; but when all three are combined antithrombin activity is regenerated. Klein and Seegers[45] have found that defibrinated plasma produces 24 per cent inactivation of purified bovine thrombin in the presence or absence of heparin; whole plasma inactivates 41 per cent and heparin plus whole plasma inactivates 71 per cent. They have shown that heparin promotes the adsorption of thrombin on fibrin and then postulated that fibrinogen is the cofactor of heparin. However, Astrup and Darling[46] have found that heparin cofactor activity (proantithrombin) remains in certain plasma frac-

tions, after fibrinogen has been removed. This, along with Howell's[47] data, indicates the existence of proantithrombin.

9. *Antithromboplastin:* Tocantins[48] has prepared an antithromboplastin from both plasma and brain thromboplastins. It may seem peculiar that thromboplastin should contain a relatively large amount of its own inhibitor, but this has been demonstrated. Coon et al[49] report that Tocantins' inhibitor reduces both accelerator globulin and plasma prothrombin levels in dogs and rabbits. Overman and Wright[50] have prepared a similar, if not identical, inhibitor. Tocantins, believing that the inhibitor has great attraction for glass surfaces, stresses the importance of avoiding glass if the inhibitor is to be demonstrated in normal blood or plasma. He states that the concentration of his inhibitor is increased in hemophilia,[51] thus explaining the prolonged coagulation time of such blood.

10. *Proantiprothrombin:* This inhibitor, more commonly known as cofactor 1 of heparin, has been recognized for years, but as yet little has been published concerning it.

11. *Antiprofibrinolysin:* This is at present only a name for the compound that would parallel the preceding one. An antifibrinolysokinase could also be postulated since the corresponding antistreptokinase has already been shown to exist.

REACTIONS IN THE CLOTTING AND LYSING MECHANISMS

These reactions must be taken up singly, but since they are so closely related one cannot ignore the overall pattern of interrelationships. In the first equation (I, fig. 1), a small amount of thrombin is formed by the reacting thromboplastin, calcium ions, and platelet factor. This reaction is slow but would go on to completion if it were not for the chain reaction it initiates. As soon as a small amount of thrombin is formed in I, it engages in II, activating plasma accelerator globulin to serum accelerator globulin. Since reaction I is proceeding at a very slow rate, the end product of II can now enter into the chain. Thus, reaction III, a livelier continuation of I, proceeds at a much faster pace producing sufficient thrombin to initiate IV, the conversion of fibrinogen to fibrin, the clot. As the fibrin is formed, it adsorbs a considerable amount of thrombin. This is the first of the competitive reactions. It removes the adsorbed thrombin, preventing further enzymatic action on fresh fibrinogen. It also helps bring about the process in reaction V by completely dispersing the proteolytic enzyme in the fibrin clot.

Fibrinolysokinase entering the circulation activates profibrinolysin to fibrinolysin (VI). The active enzyme then begins digesting fibrinogen, fibrin, and prothrombin (VII, VIII and IX). Clotting fibrinogen has a special affinity for fibrinolysin; therefore, as clots are formed they readily encompass the lytic factors which speed their physiologic resolution.

Very little is known about reactions X to XV. This inhibitor phase, which is so important in maintaining the fluid balance, is being investigated with ever increasing effort. Proantithrombin, antithromboplastin, and antifibrinolysin have been purified and the other inhibitors have been identified. Balanced equations cannot as yet be written for most of the reactions.

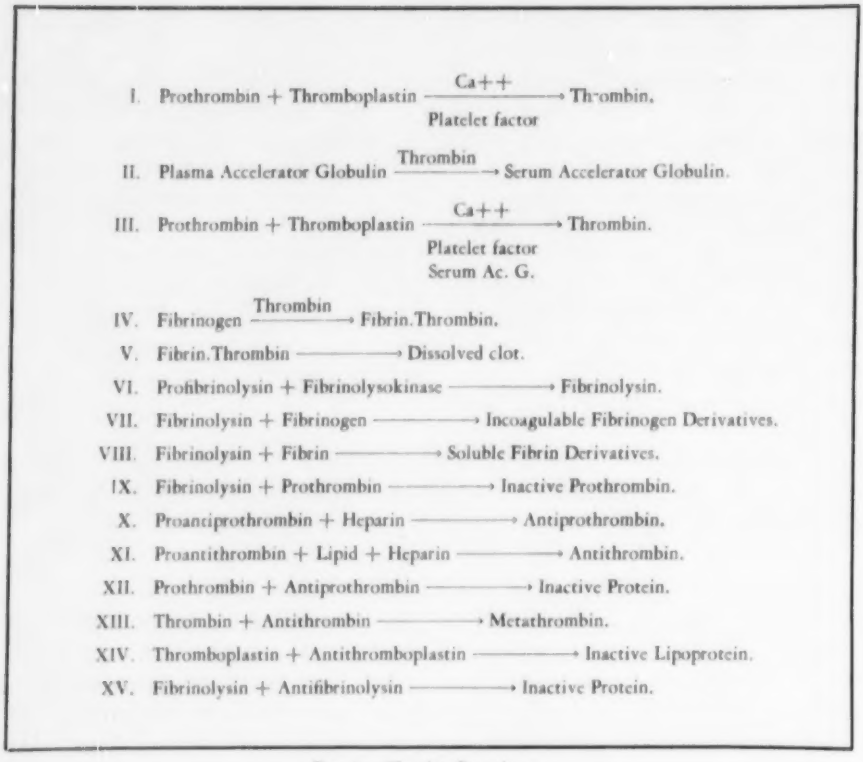
I. Prothrombin + Thromboplastin —Ca++ / Platelet factor→ Thrombin.
II. Plasma Accelerator Globulin —Thrombin→ Serum Accelerator Globulin.
III. Prothrombin + Thromboplastin —Ca++ / Platelet factor, Serum Ac. G.→ Thrombin.
IV. Fibrinogen —Thrombin→ Fibrin.Thrombin.
V. Fibrin.Thrombin → Dissolved clot.
VI. Profibrinolysin + Fibrinolysokinase → Fibrinolysin.
VII. Fibrinolysin + Fibrinogen → Incoagulable Fibrinogen Derivatives.
VIII. Fibrinolysin + Fibrin → Soluble Fibrin Derivatives.
IX. Fibrinolysin + Prothrombin → Inactive Prothrombin.
X. Proanciprothrombin + Heparin → Antiprothrombin.
XI. Proantithrombin + Lipid + Heparin → Antithrombin.
XII. Prothrombin + Antiprothrombin → Inactive Protein.
XIII. Thrombin + Antithrombin → Metathrombin.
XIV. Thromboplastin + Antithromboplastin → Inactive Lipoprotein.
XV. Fibrinolysin + Antifibrinolysin → Inactive Protein.

FIG. 1. Clotting Reactions.

Reactions X to XV are competitive with certain reactions in the clotting and lysing processes. Heparin is removed from the circulation by X and XI, reducing the danger inherent in excess free circulating anticoagulant from mast cells; XII competes with I, III and IX; XIII, along with the adsorption indicated in IV, competes with the production of excessive amounts of fibrin, which might otherwise result in thromboembolic phenomena; XIV competes with I and III to help keep the latter reactions under control; XV competes with VII, VIII and IX, inactivating excessive amounts of the proteolytic enzyme.

The dynamic equilibrium is now apparent. Visualize each of these reactions proceeding at a slow rate, one counteracting or aiding the other competitively. Several of these reactions have end products which do not enter into another coagulation reaction, for example the fibrinogen and fibrin derivatives. These compounds are recycled through tissue enzyme systems to aid in the synthesis of new active proteins or eliminated from the circulation as metabolites. One now has the circulating blood in a dynamic equilibrium ready to be triggered by the physiologic or pathologic environment into one type or another of activity. This change in the dynamic equilibrium may save the life of, or cause the death of, the entire organism.

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GENERAL PRACTICE CLINICS

Abstracts from the Symposium on Antibiotics

The following abstracts are of some of the papers that were delivered at the SYMPOSIUM ON ANTIBIOTICS in Washington, D.C., October 28–30, 1953. This symposium was sponsored by the Department of Health, Education, and Welfare, Division of Antibiotics of the Food and Drug Administration in collaboration with the journal, ANTIBIOTICS AND CHEMOTHERAPY. The papers delivered at the Antibiotic Symposium are printed *in toto* in the *Antibiotics Annual 1953–1954*, published by Medical Encyclopedia, Inc.*

1. *The Pharmacology of Tetracycline.* R. W. CUNNINGHAM AND L. R. HINES, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

Tetracycline is a highly active, broad spectrum antibiotic. The free base characteristically forms salts, which may be crystallized with both acids and bases. It has a low order of toxicity and almost no discernible side reactions. Rats and mice tolerate single oral doses of 2000 mg./Kg. without observable effects. The intravenous LD_{50} in mice is 170 mg./Kg. and in rats, 220 mg./Kg. Eight daily, intraperitoneal injections (mice, 50 and 100 mg./Kg.) revealed no toxic manifestations. A similar experiment in rats duplicated these results. The antibiotic was given intravenously to 4 dogs twice daily (10 mg./Kg., 5 days per week) for a total of 32 injections. Routine function tests, blood chemistry determinations, clotting time, and complete blood counts did not differ significantly from pre-dosing values. Two daily oral doses (100 mg./Kg., 4 dogs, 5 days per week, 9 weeks) resulted in no significant toxic manifestations.

Multiple intravenous injections of 10 mg./Kg. at 15 to 20 minute intervals in anesthetized dogs had no adverse effect on blood pressure, respiration, heart rate, or the usual circulatory responses to epinephrine, histamine, acetylcholine, and right vagal stimulation. The antibiotic is free of anticoagulant, anticonvulsant, antispasmodic, and sedative properties.

2. *Tetracycline—Microbiological, Pharmacological and Clinical Evaluation.* A. R. ENGLISH, S. Y. P'AN, J. F. GARDOCKI, AND W. A. WRIGHT, Charles Pfizer and Company, Inc., Brooklyn, New York.

Tetracycline, a new antibiotic closely related to chlortetracycline [Aureomycin] and oxytetracycline (Terramycin) has been found to possess interesting biologic activity. In the course of *in vitro* antibacterial spectrum studies, a great variety of pathogenic microorganisms have been checked for their sensitivity to this new

* Medical Encyclopedia, Inc., 30 East 60th St., New York 22, New York.

antibiotic agent. *In vivo* activity has been demonstrated in streptococcal, diplococcal, *Salmonella*, and *Klebsiella* infections in mice. Antibiotic serum levels have been checked in experimental animals using the intravenous, intramuscular and oral routes of administration. The pharmacologic studies of tetracycline reveal it to have a toxicity somewhat similar to Aureomycin and showing limited pharmacodynamic activity. The results of clinical evaluation along with blood levels in humans are presented.

3. *Prophylaxis Against Group A Streptococci in Rheumatic Fever Patients by the Use of Single Monthly Injections of N,N′ Dibenzylethylenediamine Dipenicillin G (Bicillin). Progress Report.* GENE H. STOLLERMAN, Irvington House and the Department of Medicine, N.Y.U. College of Medicine.

N,N′ Dibenzylethylenediamine dipenicillin G (Bicillin) was administered once every four weeks as a single intramuscular injection in a dose of 1.2 million units to 133 outpatients who had recently recovered from rheumatic fever. The results of the first year's study of this method of prophylaxis against group A streptococci are as follows:

There were no recurrences of rheumatic fever in 1,411 patient-months of observation. Clinical streptococcal pharyngitis was not encountered. Of 1,267 routine, monthly throat cultures, 3 were positive for group A streptococci (in 2 patients). Of 1,261 determinations of antistreptolysin O serum titers, a significant rise occurred in only 2 patients (those with positive throat cultures). No serious toxic reactions, systemic or local, were observed including 152 additional hospitalized patients who received 1,220 injections of Bicillin according to the same regimen. Injections had to be permanently discontinued in only one patient. Six others had transient, mild skin rashes. Seventeen had a brief, mild febrile reaction. Local tenderness and induration were common but transient. No abscess formation occurred at injection sites.

The results to date compare favorably with those obtained by treatment of a comparable group of rheumatic fever patients with daily oral doses of either 1.0 Gm. of sulfadiazine or 200,000 units of penicillin G.

4. *The Prophylaxis of Acute Respiratory Infections with Oral Penicillin or Chlortetracycline (Aureomycin).* Personnel of Naval Medical Research Unit #4, U. S. Naval Training Center, Great Lakes, Illinois.

Clinical and bacteriologic studies were made at weekly intervals on groups of Navy recruits who received a daily oral dose of either 100,000 units of procaine penicillin, 250 mg. of chlortetracycline, or a placebo for six weeks. Streptococcal infections and influenza A were epidemic during the period of prophylaxis.

Both antibiotics were highly effective in preventing streptococcal infections. Neither altered the attack rate for symptomatic episodes unrelated to streptococci which clinically resembled common colds or influenza. However, there was an unexplained significant decrease in serologically diagnosed influenza among men given chlortetracycline. Untoward reactions were not observed with either anti-

biotic, except for the occurrence of mild diarrhea during the second week of prophylaxis in the chlortetracycline treated group. The diarrhea subsided spontaneously despite continued treatment.

Studies on randomly selected men from each treatment group revealed no changes in the composition of the bacterial flora of the nose or throat which could be related to antibiotic treatment. All strains of alpha and beta hemolytic streptococci were antibiotic sensitive. Penicillin resistant strains of staphylococci were isolated with greater relative frequency from the penicillin treated group. Chlortetracycline resistant staphylococci were found only among men who received this antibiotic.

5. *A Clinical Study of Streptohydrazid in Pulmonary Tuberculosis.* HOWARD M. PAYNE, CONSTANCE C. QUARLES, OSCAR ELLISON, K. ALBERT HARDEN, Howard University School of Medicine, Washington, D. C.

Streptohydrazid (streptomycylidene isonicotinyl hydrazine) has been studied in the Chronic Chest Disease Service of Howard University in cooperation with the laboratories of Chas. Pfizer & Co., Inc.

Biologic assay procedures have demonstrated satisfactory concentration of streptomycin and isoniazid in the plasma and spinal fluid of patients after the intramuscular injection of 1 Gm.

Clinical observation upon 87 patients is available. Of these, 46 patients received 1 Gm. of streptohydrazid daily for 10 days plus 12 Gm. of sodium PAS. The PAS was continued for two months for this group which then was given streptohydrazid, 1 Gm. twice weekly alone. Forty patients have received ten days of daily SIH and intermittent SIH, 1 Gm. twice weekly. Control regimens are compared for 37 patients.

Bacteriologic, x-ray, clinical, and toxicity observations were reported in an attempt to determine the feasibility and effect of intermittent streptohydrazid administration with regard to clinical improvement, development of resistance and the incidence of toxicity.

6. *The Present Status of Bacitracin Available for Systemic (Intramuscular) Administration.* FRANK L. MELENEY AND BALBINA A. JOHNSON, Department of Surgery, Laboratory of Surgical Bacteriology, College of Physicians and Surgeons, Columbia University, and the Surgical Service of the Presbyterian Hospital, New York City.

Bacitracin prepared for systemic (intramuscular) administration has been steadily increasing in purity and decreasing in nephrotoxicity. It is now manufactured by three pharmaceutical firms.

In March, 1952, the Food and Drug Administration set up a new tentative specification for purity of 50 units per milligram and a safety test for toxicity of an LD_0 of 100 units for a 20 Gm. mouse.

During the past year, a series of 60 cases has been studied to see if these specifications and the presently available product warrant a release of bacitracin by the

Food and Drug Administration from the present requirement of use systemically "in hospitals only." Four different lots were used from each of the three manufacturers. Five patients were treated with each lot. Nephrotoxicity was measured by the amount of albuminuria and any rise in the blood urea nitrogen. In 75 per cent of the cases, the nephrotoxicity was slight. In 22 per cent it was moderate, but did not require discontinuing treatment and it was quickly reversible. In only 3 per cent of the cases was the nephrotoxicity disturbing, and that also was reversible soon after the administration of the drug was discontinued. The 2 cases showing disturbing nephrotoxicity were treated with the same lot, which had been prepared by a new process. With this process discarded, it may be expected that the bacitracin now available may be administered systemically without fear of serious nephrotoxicity, providing a certain simple directive is followed.

7. *Chloramphenicol in Chronic Ulcerative Colitis: Blood Counts Over A Four-Year Period in 67 Patients and Sensitivity Studies of Predominating Organisms in Stools.* Z. T. BERCOVITZ, 121 East 60 Street, New York, New York.

Chloramphenicol has been used in the treatment of 67 chronic ulcerative colitis patients since February, 1949. More than 23,000 Gm. of the drug have been administered. No significant changes have occurred in either the erythrocytes or leukocytes in more than 300 blood counts made in these 67 individuals. There is no correlation between the blood picture and the total amount of Chloromycetin administered, dosage schedule used, duration of therapy, or method of administration. There has been no evidence of cumulative toxic effects even though some individuals received the drug for the entire four years on a maintenance dosage program of 2 Gm. daily for a week every other week.

Sensitivity tests have been made of the predominating organisms found in stool cultures of 6 of these patients to date who have been on the chloramphenicol maintenance regime for prolonged periods. No pathogenic staphylococci have been found in any of the specimens. All of the predominating organisms, including the various forms of *E. coli*, streptococci and *B. proteus*, have exhibited sensitivity to chloramphenicol, with no evidence of having developed resistance to this antibiotic even though the patients involved have received large amounts of the drug over a long period of time.

8. *The Effect of Chloramphenicol on the Bone Marrow in Infants and Children.* JOHN DOYLE, DAVID BELL, SIDNEY ROSS, E. CLARENCE RICE, Children's Hospital of District of Columbia.

A study was conducted to determine the effect of chloramphenicol (as well as other antibiotics) on the bone marrow and peripheral blood in the pediatric age group. Fifty children were observed. A control bone marrow and peripheral blood count was obtained prior to initiation of therapy. Following this, chloramphenicol, in therapeutic dosage was administered for 7 to 10 days. After termination of therapy, another bone marrow and peripheral blood examination was performed. No discernible depressant effect of chloramphenicol on the hematopoietic system was observed in this series.

9. *Long Range Study of the Use of Broad Spectrum Antibiotics in Elderly People.* L. V. MCVAY AND D. H. SPRUNT, Institute of Pathology, University of Tennessee, Memphis, Tennessee.

The health of an elderly individual is frequently impaired by inter-current infections. These infections might be ones which a younger individual would overcome with ease. In the aged, however, they may lead to a fatal outcome.

With this in mind, the authors decided to study the effect of a broad spectrum antibiotic, chlortetracycline [Aureomycin], as a prophylactic measure on a number of elderly patients.

For this study, 400 ambulatory patients from the authors' outpatient clinic were selected. These fell into 3 main classes—cardiacs, diabetics, and pulmonics. Approximately one half of these were given a placebo which contained vitamins and minerals, and the other half were given vitamins and minerals plus 500 mg. Aureomycin. The two capsules were identical in appearance. Neither the patients nor the physician knew which were on the placebo and which were on the Aureomycin. These patients have been studied with a number of clinical and laboratory tests. The results have been striking. The ones receiving the Aureomycin are much better in almost every respect than the controls.

All the patients have been extensively studied from a bacteriologic standpoint and it is quite interesting that no significant increase in bacterial strains resistant to Aureomycin has developed. Also, there have been no significant changes in the basic flora of the alimentary tract.

10. *Laboratory and Clinical Experience with Dibenzylamine Penicillin G.* C. H. MANN, C. R. REIN, P. A. BUNN, S. FLAX, AND C. MORSEBURY, Bristol Laboratories, Inc., New York, N. Y., Department of Dermatology and Syphilology, New York University Post Graduate Medical School, New York, N. Y., Department of Medicine, State University of New York, Syracuse, New York.

The development of a new salt of penicillin, viz., Dibenzylamine Penicillin G, is the basis of this report which reviews laboratory studies and clinical experience with it.

Laboratory studies were directed toward the determination of penicillin serum concentrations at various intervals following the administration of three pharmaceutical formulations of Dibenzylamine Penicillin G to two significant groups of patients, one group having been tested at Bellevue Hospital, New York, N. Y., and the other at University Hospital, Syracuse, New York. The formulations include: tablets containing 200,000 units Dibenzylamine Penicillin G; tablets containing 100,000 units Potassium Penicillin G and 100,000 units Dibenzylamine Penicillin G and sterile dry fill in vials which, when reconstituted with water, provide 300,000 units Dibenzylamine Penicillin G per cc.

The clinical evaluation of Dibenzylamine Penicillin G to date has been restricted to the use of tablets, each containing 200,000 units of the penicillin salt alone. Case reports of representative microbial infections treated with Dibenzylamine Penicillin are presented.

11. *The Action of Streptomycin-Bacitracin-Polymyxin Combinations.* E. LOUGHLIN, F. R. CUSUMANO, C. W. PRICE, Bio Ramo Drug Company, Inc., Baltimore, Maryland.

Investigations were conducted into the action of streptomycin-bacitracin-polymyxin combinations against the common skin bacteria including the usually refractory *Pseudomonas-Proteus* groups. Following these studies, surgical gauze was impregnated with this combination and further studies of its ability to reduce bacterial counts and prevent frank infections in artificially contaminated wounds were made. In general, viable bacteria disappeared from these wounds within one to two hours and were absent at the forty-eighth hour with no instances of infection noted. This was in sharp contrast to the control wounds in which the bacteria multiplied rapidly and frank infections occurred in 5 to 40 per cent of the cases.

Carefully controlled clinical observations over a three year period show that: (1) the expected instances of sensitivity to the antibiotic components of this combination did not materialize; (2) the wide range and rapid activity against bacteria makes this combination an ideal prophylactic agent in accidental and surgical wounds; (3) a therapeutic potential exists in controlling secondary infections in a variety of ulcers and chronic skin conditions.

12. *Antimicrobial Agents—Their Activities Alone and in Combination.* GLADYS L. HOBBY, TULITA F. LENERT, AND DARIA PIKULA, Research Division of Charles Pfizer and Company, Inc., Brooklyn, New York.

The present report is concerned with observations on the action of twelve antimicrobial agents against strains of *Staphylococcus aureus, Salmonella typhi, Pseudomonas pyocyaneus, Proteus vulgaris, and Mycobacterium tuberculosis.* Three technics have been employed for demonstration of synergistic action: (1) measurement of the susceptibility of each microorganism to each antimicrobial agent alone and in the presence of subinhibitory amounts of a second agent; (2) measurement of the bactericidal action of agents or combinations of agents, and (3) measurement of the suppressive action of an antimicrobial agent or combination of agents upon experimental infections in animals. Although results obtained by all three procedures are mentioned, there is presented a detailed discussion of those obtained by the first method only.

Data were given to illustrate the frequency with which combinations of antimicrobial agents produce an effect greater than might be anticipated on the basis of the law of mass action or from the concentration of either agent used.

13. *The Problem of Antibiotic Therapy in Staphylococcal Septicemia.* ROBERT I. WISE AND WESLEY W. SPINK, Department of Medicine, University of Minnesota Hospitals and Medical School, Minneapolis, Minnesota.

The incidence of penicillin-resistant cases of staphylococcal sepsis has markedly increased since the introduction of penicillin in the management of this infection. Recently it has been shown in the authors' clinic that approximately 60 per cent

of strains of staphylococci from hospital patients are resistant to penicillin, and about 40 per cent are resistant to Aureomycin and oxytetracycline. The choice of antibiotics in the management of staphylococcal infection with positive blood cultures is one of the most serious therapeutic problems.

Over a period of 18 months in 1951 to 1953, 23 severe cases of staphylococcal sepsis have been studied and treated at the University of Minnesota and affiliated hospitals. An analysis of the clinical features was presented. Resistance of the causative organism to the antibiotics was demonstrated *in vitro* and was a major factor in therapeutic failure.

14. *Clinical Observations on the Use of Erythromycin.* EMITT H. SHOEMAKER AND ELLARD M. YOW, Department of Internal Medicine, Baylor University College of Medicine and The Ben Taub Infectious Disease Laboratory, Jefferson Davis Hospital, Houston, Texas.

Fifty patients with severe infections were treated with the oral and parenteral forms of erythromycin. Observations are presented on the results of these studies. There was a favorable response except in three patients with endocarditis, and in two patients with staphylococcal empyemia. The dose used was 25 mg./Kg./24 hours. In the beginning oral capsules of erythromycin were given, but later specially coated tablets were found to have a more consistent antibacterial effect and produced less nausea.

There were no serious local or systemic reactions from the parenteral administration of the drug. When administered orally, there were no serious side reactions, but nausea, mild cramping abdominal pain, and diarrhea occurred in about one third of the cases. The greatest value of erythromycin was felt to be in the treatment of penicillin-resistant staphylococcal infections. It has also been useful in preventing the emergence of organisms resistant to streptomycin.

15. *The Therapeutic Effect of Erythromycin in Endocarditis.* LLOYD C. JONES AND ELLARD M. YOW, Department of Internal Medicine, Baylor University College of Medicine and The Ben Taub Infectious Disease Laboratory, Jefferson Davis Hospital, Houston, Texas.

While there have been striking advances in the therapy of endocarditis since the discovery of penicillin, there are still therapeutic failures in about 20 per cent of cases. The present study was undertaken in an attempt to evaluate the effect of erythromycin alone and in combination with other antibiotics in the treatment of patients with endocarditis failing to respond to previous therapy. Nine patients were treated, including one with an acute micrococcic endocarditis, another with subacute micrococcic endocarditis, and seven with streptococcal endocarditis.

Erythromycin was administered alone to 3 patients, resulting in a transient suppression of the infection in one. It was given in combination with streptomycin to 7 patients. There was bacteriologic and clinical evidence of cure in 5 of these patients. One died of heart failure during therapy, and in another, the organism

was found to be resistant to streptomycin. This patient responded to treatment with erythromycin and bacitracin.

It may be concluded from this study that erythromycin alone is of little value in the treatment of endocarditis. When used in combination with streptomycin against susceptible organisms it was effective in 5 patients.

16. *Laboratory Experience and Tolerance Studies with the New Oral Stable Suspension of Potassium Penicillin G.* C. H. MANN, PAUL A. BUNN, C. R. REIN, C. MORSEBURY, AND S. FLAX, Bristol Laboratories, Inc., New York, N. Y.; Dept. of Medicine, State University of New York, Syracuse, New York; Dept. of Dermatology and Syphilology, New York University Post Graduate Medical School, New York, New York.

This study deals with the testing of the new oral stable suspension of Potassium Penicillin G. The laboratory evaluation of the product consists of the determination of penicillin serum concentrations at various intervals following the administration of one teaspoonful of the suspension containing 300,000 units of penicillin to a representative group of patients at two different hospitals. The results obtained are compared with those observed from the same oral dosage of Potassium Penicillin G in water and with the oral administration of 300,000 units of Dibenzylethylene diamine dipenicillin G in a water vehicle. Tolerance studies conducted with the oral suspension of penicillin showed that practically all of the patients receiving the product tolerated it well.

17. *Evaluation of Dibenzylethylenediamine Penicillin in the Prevention of Rheumatic Fever by Treatment of the Preceding Streptococcal Illness.* ROBERT CHAMOVITZ, 1st Lt. USAF (MC) AND FRANCIS J. CATAZARO, 1st Lt. AUS (MC), Streptococcal Disease Laboratory, Warren Air Force Base, Wyoming, and Department of Preventive Medicine, Western Reserve University, School of Medicine, Cleveland, Ohio.

The introduction of dibenzylethylenediamine penicillin,* a long acting repository preparation, afforded the opportunity to study an antibiotic that in one injection might prevent rheumatic fever by treatment of the preceding streptococcal illness.

This is a preliminary report on the study of 241 patients with exudative pharyngitis. One hundred and thirty-two of these patients received a single intramuscular dose of 1,200,000 units of dibenzylethylenediamine penicillin. One hundred and nine of these patients received symptomatic therapy and served as controls. There were 2 cases of acute rheumatic fever and 1 case of acute glomerulo-nephritis from the control group, whereas there were no such cases in the treated group.

There was marked inhibition of antistreptolysin formation demonstrated in the treated patients.

* Supplied as Bicillin by Wyeth, Inc., Philadelphia, Pa.

Of the treated patients examined 21 days from the onset of their illness, only 1 patient had beta hemolytic streptococci isolated from a culture of the throat, whereas 84.8 per cent of the control patients had beta hemolytic streptococci isolated from cultures of the throat. These bacteriologic results show that dibenzylethylenediamine penicillin was more effective than other therapeutic regimens in the eradication of the infecting streptococcus.

Evidence from previous studies appears to indicate that eradication of the infecting streptococci is essential in the prevention of rheumatic fever. The results of this study indicate that further experience with a single intramuscular injection of dibenzylethylenediamine penicillin in the dosage employed will prove effective in the prevention of rheumatic fever.

18. *A New Broad Spectrum Antibiotic Product of the Tetracycline Group.* P. PAUL MINIERI, MELVIN C. FIRMAN, A. G. MISTRETTA, ANTHONY ABBEY, CLARK E. BRICKER, NEIL E. RIGLER, AND HERMAN SOKOL, Antibiotics Research Division, Heyden Chemical Corporation, Princeton, N. J.

An organism has been isolated from a Texas soil which produces a broad spectrum antibiotic apparently belonging to the tetracycline group. High yielding mutants of this organism have been obtained which produce the antibiotic in both synthetic and natural media. The antibiotic can be purified by countercurrent distribution of the crude material obtained after a solvent extraction of the acidified fermentation broth.

The antibiotic resembles oxytetracycline and chlortetracycline in physical properties, antibacterial spectra, cross resistance, lack of toxicity, and ability to protect animals against experimental infections. However, it can be clearly distinguished from both of these substances—the infra-red spectrum and countercurrent distribution studies at once indicating a general similarity but specific differences. The antibiotic is an amphoteric compound; a crystalline-free base and a crystalline hydrochloride have been obtained. A further discussion of physical, chemical, antibacterial, and pharmacologic properties of the antibiotic are given.

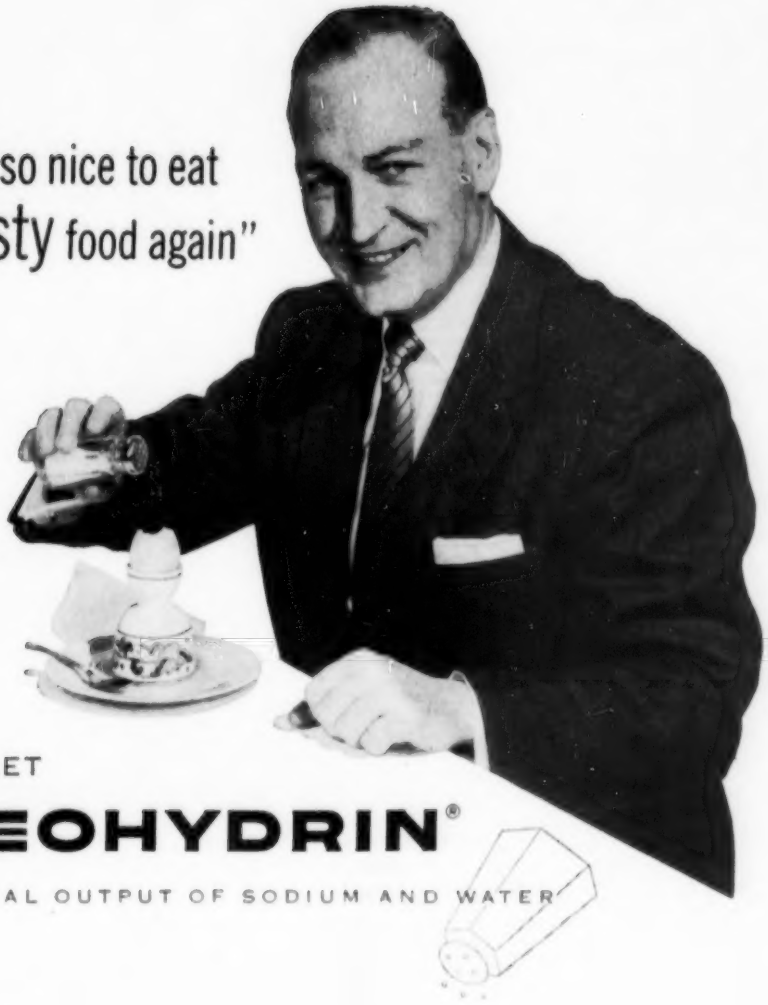
19. *The Successful Treatment with Erythromycin of Hemophilus Influenzae Bacteremia and Pneumonia: A Case Report.* JOHN NASOU AND M. J. ROMANSKY, George Washington University Medical Division, D. C. General Hospital and the Department of Medicine, George Washington University School of Medicine.

Hemophilus influenzae infections have been treated with every antibiotic in current use, and present concepts of therapy revolve around the use of various combinations of sulfadiazine, streptomycin, and the broad spectrum antibiotics. Recent literature indicates that strains of *Hemophilus* are sensitive to erythromycin *in vitro*. The following represents a case of *Hemophilus influenzae* pneumonia and bacteremia in which erythromycin therapy was begun before the etiological agent was discovered.

R. M., a 46 year old white, married male, was admitted to the District of Columbia General Hospital on August 6, 1953, complaining of pleuritic pain in the lower, left chest anteriorly and severe cough productive of yellow sputum of one day's duration. Physical examination revealed the temperature to be 103 F., the pulse 120 per minute, and respiratory lag of the left hemithorax. There was increased tactile fremitus, dullness on percussion, bronchial breathing, and E to A change over the left lung base indicating the presence of pneumonia, which was verified by x-ray of the chest. Total white blood cell count was 5000 per cu. mm., differential of 72 polymorphonuclears, 27 lymphocytes, and 1 monocyte, hematocrit of 46 mm., and urinalysis revealed no abnormal findings. Three blood cultures were obtained on admission. Treatment with erythromycin 500 mg. per os every four hours (total of 3 Gm. daily) was started immediately. The blood cultures drawn on admission showed *Hemophilus influenzae*, type B, five days later. A sputum specimen at this time also showed *Hemophilus influenzae*. There was progressive decrease of fever to normal temperature eight days after admission. At this time a chest film revealed further clearing of the original lesion, but a new density appeared in the middle third of the left lung. Despite this, the patient remained afebrile for the remainder of his hospital stay and the density resolved by the fifteenth hospital day. Repeated sputa and two gastric washings were negative for acid fast organisms. Subsequent blood cultures were likewise negative. Erythromycin was discontinued on the twenty-first hospital day; chest film on the twenty-fifth day revealed complete clearing of the pneumonia, and the patient was discharged.

20. *Ruticin, A New Antibiotic.* W. P. FISHER, JESSE CHARNEY, ROY A. MACHLOWITZ, JAMES E. BLAIR, AND ALFRED A. TYTELL, Sharp & Dohme Research Division, Merck & Co., West Point, Pa.

A new antibiotic, ruticin, has been found to be produced by a culture of a *Streptomyces* closely resembling *Streptomyces rutgersensis*. The antibacterial spectrum of ruticin includes *Bacillus subtilis*, *Staphylococcus aureus*, and *Proteus vulgaris*. The antibiotic was produced in a simple medium consisting of salts, glutamic acid, and dextrin. In deep culture, the active substance is very rapidly destroyed by mycelium in the absence of oxygen. The active crystalline antibiotic is also enzymatically inactivated by washed mycelium and by mouse liver homogenate. Ruticin is an acid and was isolated by a solvent extraction procedure. It was obtained as orange needle-like crystals by repeated crystallization from methanol. The ultraviolet spectrum of ruticin exhibits maxima at 364 and 262 mμ with a minimum at 227 mμ. Crystals of totally inactive material have been obtained which exhibit an identical ultraviolet spectrum. The free acid is soluble in methanol, ethanol and ethyl acetate, while only sparingly soluble in water. The sodium salt of ruticin is soluble in water, methanol and ethanol and is insoluble in ethyl acetate and less polar solvents. The crystalline antibiotic is unstable even when stored at −20 C. over a period of months. The LD_{50} for mice by the intravenous route is 25 mg./Kg. The fact that ruticin is rapidly inactivated by metabolizing tissue may account for the failure to obtain positive therapy in mouse protection tests.



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